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PROCEEDINGS AND ABSTRACTS

SECOND MEETING OF THE ALZHEIMER'S IMAGING CONSORTIUM

Stockholm Fairgrounds, Stockholm, Sweden, July 20, 2002☆

Executive Committee of the Alzheimer's Imaging Consortium: Michael W. Weiner, M.D. (Chair); Marilyn S. Albert, Ph.D.; Charles S. DeCarli, M.D.; Mony de Leon, Ph.D.; Nicholas C. Fox, M.D.; Norman C. Foster, M.D.; Clifford R. Jack, Jr., M.D.; William J. Jagust, M.D.; Eric M. Reiman, M.D.; Philip Scheltens, M.D.; Gary W. Small, M.D.; Hilkka Soininen, M.D., Ph.D.; Lars-Olof Wahlund, M.D., Ph.D.

Advisors: Ronald C. Peterson, M.D., Ph.D.; Leon J. Thal, M.D.; Zaven Khachaturian, Ph.D.

Introduction:

On July 20, 2002, the Alzheimer's Imaging Consortium held its second meeting, just prior to the World's Alzheimer's Congress, in Stockholm, Sweden. This meeting consisted of invited talks, abstract presentations, posters, and panel discussions, all focused on the use of various imaging techniques for investigation, diagnosis, early detection, and therapy monitoring of Alzheimer's disease and other related dementia-causing disorders.

The overall highlight of this meeting was the general consensus that various types of imaging are now recognized as playing a greater and greater role in Alzheimer's disease research, evidenced by the large number of abstracts submitted, and heavy attendance (over 120 participants). Invited talks and other highlights included the following: David Knopman from Mayo Clinic summarized the role of imaging in diagnosis of Alzheimer's; William Klunk from Pittsburgh and Jorge Barrio from Los Angeles both discussed use of PET tracers to detect brain amyloid in AD; Marilyn Albert from Harvard reviewed her work concerning the role of entorhinal cortex volume for predicting progression of cognitive decline; Reisa Sperling from Harvard reviewed the role of fMRI in Alzheimer's research; Russell Katz from the FDA summarized the potential role of imaging in evaluating treatments for Alzheimer's disease for FDA approval; Neil Buckholz from the National Institute on Aging summarized progress concerning the development of an Alzheimer's Neuroimaging Initiative, to be cofunded by the NIA and the pharmaceutical industry; and a panel of representatives from several pharmaceutial companies discussed various aspects of this initiative. In addition to the above noted talks, there were a large number of talks selected from abstract presentations, and an even larger number of posters. The entire program of the meeting and all of the submitted abstracts are presented as follows.

ALZHEIMER'S IMAGING CONSORTIUM

Stockholmsmassan AB

Massvagen 1

Conference Room: K-21

Stockholm/Alvsjo

Welcome to the Alzheimer's Imaging Consortium this July 20, 2002, at the Stockholm International Fairs—prior to the opening of the 8th International Conference on Alzheimer's Disease and Related Disorders.

Meeting Agenda: This meeting will focus on the use of MRI, PET and SPECT imaging for early detection, diagnosis, and therapy monitoring of Alzheimer's disease and other dementias. The following program consists of invited talks, oral abstract presentations, posters, breakfast, coffee breaks and lunch. Posters will be available for viewing during coffee breaks and lunch—there will be over 50 poster presentations.

The Excom:

Philip Scheltens, Vrije U Amsterdam, The Netherlands.

Charles S. DeCarli, University of California at Davis, Davis, CA, USA.

Hilkka Soininen, M.D., Ph.D., University of Kuopio, Kuopio, Finland.

☆ For further information concerning the Alzheimer's Imaging Consortium, contact Dr. Michael Weiner (e-mail: mweiner@itsa.ucsf.edu).

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Clifford R. Jack, Jr., M.D., Mayo Clinic, Rochester, MN, USA.

Mony de Leon, New York University, New York, NY, USA.

Nicholas C. Fox, M.D., University of London, London, UK.

Gary W. Small, University of California at Los Angeles, Los Angeles, CA. USA.

Eric M. Reiman, M.D., Good Samaritan Regional Medical Center, Phoenix, AZ, USA.

Lars-Olof Wahlund, M.D., Ph.D., NEROTEC, Karolinska Institutet, Stockholm, Sweden.

Marilyn S. Albert, Ph.D., Harvard University, Boston, MA, USA.

William J. Jagust, M.D., UC Davis, Sacramento, CA, USA.

Advisors to the Excom:

Leon J. Thal, M.D., University of California at San Diego, San Diego, CA, USA.

Ronald C. Petersen, M.D., Ph.D., Mayo Clinic, Rochester, MN, USA.

PROGRAM

8.30: *Introduction*: Michael Weiner, UCSF, San Francisco, CA, USA.

8.35: *Plenary Talk: The Clinical Diagnosis of Dementia: A Starting Point for Defining the Role of Imaging*: David Knopman, Mayo Clinic, Rochester, MN, USA.

Amyoid Imaging: Chairs: Lars-Olof Wahlund, M.D., Ph.D., NEROTEC, Karolinska Institutet, Stockholm, Sweden; Marilyn S. Albert, Ph.D., Harvard University, Boston, MA, USA.

9.00: *Imaging Amyloid with PET* (Invited): Jorge R. Barrio, University of California at Los Angeles, Los Angeles, CA, USA.

9.17: *Challenges Faced in the Development of Human In Vivo Amyloid-Imaging Agents* (Invited): William E. Klunk, M.D., Ph.D., Chester A. Mathis, Ph.D., University of Pittsburgh, Pittsburgh, PA, USA.

9.34: *Molecular Targeting of Alzheimer's Amyloid Plaques for Contrast-Enhanced Magnetic Resonance Imaging*: J.F. Poduslo, T.M. Wengenack, G.L. Curran, T. Wisniewski, E.M. Sigurdsson, S.I. Macura, B.J. Borowski, C.R. Jack, Jr., Mayo Clinic, Rochester, MN; New York University School of Medicine, New York, NY, USA.

9.39: *Discussion*: Steven G. Younkin, M.D., Ph.D., Mayo Clinic, Jacksonville, FL, USA.

Early Detection of AD: Chairs: Gary W. Small, University of California at Los Angeles, Los Angeles, CA; Eric M. Reiman, M.D., Phoenix, AZ, USA.

9.49: *Early Detection of AD* (Invited): Marilyn S. Albert, Ph.D., Harvard University, Boston, MA, USA.

10.06: *Volumetry of the Hippocampus and Entorhinal Cortex in Mild Cognitive Impairment and Early Diagnosis of AD*: C. Pennanen, M. Kivipelto, S. Tuomainen, P. Hartikainen, T. Hanninen, M. Hallikainen, M. Vanhanen, M. Laakso, A. Nissinen, E.-L. Helkala, P. Vainio, K. Partanen, H. Soininen, Department of Neuroscience and Neurology, Department of Neurology, Department of Radiology, Department of Public Health, University of Kuopio, Kuopio University Hospital, Kuopio; National Institute of Public Health, Helsinki, Finland.

10.18: *Longitudinal Declines of Gray Matter in Cognitively Normal Apolipoprotein E Epsilon4 Homozygotes and Heterozygotes Evaluated by Voxel-Based MRI Morphometry*: G. Alexander, K. Chen, E.M. Reiman, R.J. Caselli, D. Lewis, D. Bandy, A. Prouty, Psychology Department, Arizona State University, Tempe; PET Center, Good Samaritan Regional Medical Center, Phoenix; Psychiatry Department, University of Arizona; Neurology Department, Mayo Clinic, Scottsdale; Arizona Alzheimer's Research Center, Phoenix, AZ, USA.

10.30: *Longitudinal Measures of Hippocampal Volume and CSF Measures of Phospho-Tau and Amyloid Beta: Early Markers for Alzheimer's Disease*: M. de Leon, S. Segal, S. DeSanti, P.D. Mehta, R. Zinkowski, C. Tarshish, A. Convit, C. Caraos, H. Rusinek, W. Tsui, L.A. Saint Louis, J. DeBernardis, D. Kerkmanand, P. Davies, Center For Brain Health, New York University School of Medicine, New York; Institute for Basic Research, Staten Island; Albert Einstein College of Medicine, Bronx, NY; Molecular Geriatrics, Vernon Hills, IL, USA.

10.42: *Discussion*: Gunhild Waldemar, M.D., Department of Neurology, Rigshospitalet, Section 6702, Copenhagen University Hospital, Copenhagen, Denmark.

10.52: Coffee Break: VIEWING AND DISCUSSING POSTERS IS ENCOURAGED

FMRI of AD: Chairs: Hilkka Soininen, M.D., Ph.D., University of Kuopio, Kuopio, Finland; Michael S. Mega, University of California at Los Angeles, Los Angeles, CA, USA.

11.12: *Functional MRI Studies in Early Alzheimer's Disease*: R. Sperling, E. Chua, J. Bates, D. Schacter, D. Rentz, D. Greve, A. Dale, B. Rosen, M. Albert, Brigham and Women's Hospital, Memory Disorders Unit, Boston; Massachusetts General Hospital, Charlestown; Harvard University, Cambridge, MA, USA.

11.29: *FMRI in the Diagnosis of Early Alzheimer's Disease*: M.M. Machulda, B. Borowski, H.A. Ward, R.C. Petersen, D. Knopman, B.F. Boeve, C.R. Jack, Jr., Mayo Clinic, Rochester, MN, USA.

11.41: *Alterations in Brain Activation upon Cholinergic Enhancement with Rivastigmine in Alzheimer's Disease*: S. Rombouts, F. Barkhof, C.S. van Meel, P. Scheltens, Alzheimer Center VU Amsterdam, The Netherlands.

11.53: *Discussion*: Rachelle S. Doody, M.D., Ph.D., Baylor College of Medicine, Houston, TX, USA.

12.00: Lunch Provided on Site for Participants: VIEWING AND DISCUSSING POSTERS IS ENCOURAGED

Diagnosis of AD: Chairs: Clifford R. Jack, Jr., M.D., Mayo Clinic, Rochester, MN; Jeffrey A. Kaye, M.D., University of Oregon, Portland, OR, USA.

1.00: *Inter-Rater Reliability and Diagnostic Accuracy of FDG-PET is Superior to Clinical History and Examination in Dementia*: N.L. Foster, J.L. Heidebrink, C.M. Clark, W.J. Jagust, S.E. Arnold, N.R. Barbas, C.S. DeCarli, R.S. Turner, R.A. Koeppe, R. Higdon, S. Minoshima, Ann Arbor, MI; Philadelphia, PA; Sacramento, CA; Seattle, WA, USA.

1.12: *Automated Whole-Brain Atrophy Assessment: Effects of Aging and Dementia Status*: A.L. Snyder, L. Williams, J.C. Morris, R.L. Buckner, Washington University; Howard Hughes Medical Institute at Washington University, St. Louis, MO, USA.

1.24: *White Matter Hyperintensities, Hippocampal Volume and Memory in a Community Cohort*: W. Jagust, C. Wu, C. Petkov, J. Eberling, D. Mungas, M. Haan, University of California at Davis, Sacramento, CA; University of Michigan, Ann Arbor, MI, USA.

1.36: *Discussion: What is the role of imaging (PET MRI) in the diagnosis of AD?*

Longitudinal Imaging Studies: Chairs: Mony de Leon, New York University, New York, NY, USA; Philip Scheltens, Vrije U Amsterdam, The Netherlands.

1.46: *Measuring Rates of Brain Atrophy with Serial MRI: Methodologic Considerations*: J.L. Gunter, M. Shiung, R.C. Petersen, C.R. Jack, Jr., Department of Diagnostic Radiology and MRI Laboratory, Mayo Clinic, Rochester, MN, USA.

1.58: *Hippocampus and Entorhinal Cortex Differ in Age-Related Atrophy*: N. Schuff, A.-T. Du, J.H. Kramer, B. Reed, M. Krishnan, D. Sacrey, B.L. Miller, H.L. Rosen, K. Yaffe, W.J. Jagust, H.C. Chui, M.W. Weiner, VA Medical Center; University of California at San Francisco, San Francisco; University of California at Davis, Martinez; University of Southern California, Los Angeles, CA, USA.

2.10: *Longitudinal Changes in Brain and White Matter Hyperintensity Volumes Among Elderly Male Twins from the NHLBI Twin Study*: C. Decarli, G.E. Swan, T. Reed, P.A. Wolf, D. Carmelli, University of California at Davis, Davis, CA, USA.

2.22: *Do Rates of Cerebral Atrophy in Alzheimer's Disease Accelerate?*: J.C. Janssen, D.C. Chan, R. Jenkins, J. Whitwell, H. Watt, C. Frost, N.C. Fox, M.N. Rossor, Dementia Research Group, Department of Clinical Neurology, Institute of Neurology, London, UK.

2.34: *Discussion: Role of longitudinal imaging in early detection, diagnosis and treatment trials.*

Animal Imaging Studies: Chairs: Charles S. DeCarli, U.C. Davis, Davis, CA; Susan M. Resnick, NIA, Baltimore, MD, USA.

2.44: *MRI Assessment of Neuropathology in an Animal Model of Alzheimer's Disease*: J.A. Helpern, T. Wisniewski, K. Duff, V.V. Dyakin, M.J. de Leon, B. Ardekani, O. Wolf, C.A. Branch, J. O'Shea, J. Wegiel, A. Bogart, S.-P. Lee, M.F. Falangola, R.A. Nixon, The Nathan Kline Institute, Orangeburg; New York University School of Medicine, New York, NY, USA.

2.56: *Selective Vulnerability of Hippocampal Subregions to Human Amyloid Proteins and Aging Identified by MRI in Mouse Models of Alzheimer's Disease*: S. Small, R. Mekle, N. Bowens, T. Brown, G.-Q. Yu, H. Ordanza, G. Malleret, E.R. Kandel, D. Westaway, C. Janus, P. St. George Hyslop, L. Mucke, Taub Institute for Research on Alzheimer's Disease and the Aging Brain and the Center for Neurobiology and Behavior, Columbia University, New York, NY; Gladstone Institute of Neurological Disease and University of California, San Francisco, CA, USA; Centre for Research in Neurodegenerative Diseases, University of Toronto, Canada.

3.08: Coffee Break: VIEWING AND DISCUSSING POSTERS IS ENCOURAGED

Surrogate Imaging Markers: Chairs: Nicholas C. Fox, M.D., University of London, London, UK; Scott A. Small, Columbia University, New York, NY, USA.

3.28: *Use of Imaging Surrogates in CNS Disease: Lessons from MS* (Invited): Frederik Barkhof, Image Analysis Center, Vrije U Medical Centre, Amsterdam, The Netherlands.

3.45: *Role of Imaging Surrogates in Evaluation of Treatments for Alzheimer's Disease: FDA Perspective* (Invited): Russell Katz, M.D., Food and Drug Administration, Rockville, MD, USA.

4.05: *Discussion*

Consensus Statement of Neuroimaging Work Group:
Chair: Zaven Khachaturian, KRA Associates, Potomac, MD, USA.

4.15: *Introduction*: William Thies, Alzheimer's Association, Chicago, IL, USA.

4.15: *Clinical MRI*: Charles S. Decarli, UC Davis, Davis, CA, USA.

4.25: *Research MRI*: Philip Scheltens, Vrije U, Amsterdam, The Netherlands.

4.35: *PET*: Gary Small, UCLA, Los Angeles, CA, USA.

4.45: *Discussion*

4.50: *Panel Discussion: The role of imaging in evaluation of treatments for Alzheimer's disease.* Chair: Michael W. Weiner, M.D., VA Medical Center, San Francisco, CA, USA.

Presentation of recent NIH meetings concerning this topic: Neil Buckholz, NIA, Bethesda, MD, USA.

Time permitting: An open discussion of panel speakers with the audience.

Panel speakers will include representatives from pharmaceutical companies including:

Richard Frank, Vice President, Experimental Medicine, Clinical Development, Pharmacia Inc.;

Richard Hargreaves, Ph.D., Senior Director, Pharmacology and Imaging, Merck, Inc.;

Peter Snyder, Ph.D., Associate Director, Clinical Technology (CNS), Pfizer, Inc.

5.20: Adjourn

(1) EVALUATION OF AN ITERATIVE PRINCIPAL COMPONENT ANALYSIS FOR DETECTING WHOLE BRAIN VOLUME CHANGE IN SMALL ANIMAL MAGNETIC RESONANCE IMAGING

K. Chen[1,2,3,8], E.M. Reiman[1,4,8], T. He[5,8], J.P. Galons[3,8], G. Stevenson[3,8], B. Hauss-Wegrzyniak[6,8], J. Valla[7,8], T.P. Trouard[3,8], G.L. Wenk[6,8], G.E. Alexander[5,8]

[1]PET Center, Good Samaritan Regional Medical Center, Departments of [2]Mathematics and [5]Psychology, Arizona State University, Departments of [3]Radiology, [4]Psychiatry, and [6]Psychology, University of Arizona, [7]Harrington Arthritis Research Center and [8]The Arizona Alzheimer's Research Center, Phoenix, AZ, USA

Background: In order to compute changes in human brain volume from sequential magnetic resonance images (MRIs), we developed a fully automated iterative principal component analysis (IPCA) and demonstrated its ability to distinguish whole brain atrophy rates in probable Alzheimer's disease (AD) from normal aging.

Objective: To investigate the ability of the IPCA method to detect changes in whole brain volume from sequential high-resolution MRIs in laboratory mice.

Methods: A T_2-weighted mouse brain MRI was acquired on a 4.7 T/40 cm Bruker system, yielding an isotropic resolution of 100 μm. Computer simulations were used to introduce different changes in periventricular and cortical brain volume under various noise levels. With the original and simulated follow-up MRIs, IPCA was used to compute the PCA axis independent of the candidate voxel pair and determine which changes in brain volume exceeded a threshold distance above or below this axis, thus providing information about volume gain or loss, respectively.

Results: IPCA detected volume changes with high specificity and sensitivity: It detected false-positive rates less than 0.15% of whole brain volume with a threshold distance of 2.58 standard deviations, and was not appreciably affected by different noise levels. With simulated brain volume changes, IPCA detected changes in brain volume and ventricular volume as small as 0.3% of whole brain volume, and there was a strong correlation between detected and actual volume reductions ($P < 0.0001$). In addition, IPCA could be used to visualize local volume changes on the baseline MRI.

Conclusions: IPCA can be used to detect changes in brain volume from sequential MRIs in laboratory mice. If progressive changes in brain volume can be detected in transgenic mice containing one or more AD genes, MRI could be used to track the progression of AD in these laboratory animals, helping to screen candidate treatments and clarify disease mechanisms.

(2) DETECTING AN EXPERIMENTALLY INDUCED REDUCTION IN MOUSE BRAIN VOLUME USING SEQUENTIAL HIGH-RESOLUTION MRIs AND THE ITERATIVE PCA METHOD

B. Hauss-Wegrzyniak[3], K. Chen[1,2,3,4], J.P. Galons[3], G. Stevenson[3], J. Valla[1], G.L. Wenk[3], G.E. Alexander[4], E.M. Reiman[1,2,3]

[l]Harrington Arthritis Research Center, [2]Good Samaritan Regional Medical Center, [3]University of Arizona, [4]Arizona State University, and the Arizona Alzheimer's Research Center, Phoenix, AZ, USA

Background: We previously developed an automated algorithm for the computation of changes in human brain volume from sequential magnetic resonance images (MRIs) using iterative principal component analysis (IPCA), and found that it was able to distinguish whole brain atrophy rates in Alzheimer's disease (AD) from normal aging. We subsequently refined this method for the computation of changes in mouse brain volume, and found in a computer simulation that it was able to detect reductions as small as 0.3% of whole brain volume.

Objective: To evaluate the ability of IPCA to compute an experimentally induced reduction in brain volume from sequential high-resolution MRIs.

Methods: A 4.7 T/40 cm Bruker system was used to acquire three T_2-weighted MRIs (100 μm isotropic resolution) in two young mice on separate days; for 5 h prior to the third MRI, one mouse received the intrajugular infusion of a hyperosmolar mannitol infusion, known to reduce brain volume. SPM99 was used to align sequential MRIs; IPCA was used to compute the PCA axis independent of the candidate voxel pair and determine which changes in brain

volume exceeded a threshold distance above or below this axis, thus providing information about volume gain or loss, respectively.

Results: SPM successfully aligned the sequential MRIs in each mouse. IPCA detected increased ventricular volume in the third MRI in the mannitol-treated mouse but not in the control mouse.

Conclusions: IPCA can be used to investigate changes in mouse brain volume from sequential MRIs. If it can demonstrate abnormally high brain atrophy rates in transgenic mice containing one or more AD genes, this technique could provide a non-invasive indicator of AD in these laboratory animals, helping to screen candidate treatments, and helping to clarify disease mechanisms.

(3) FEASIBILITY OF LIMITED-RESOLUTION, NON-INVASIVE FUNCTIONAL BRAIN IMAGING IN A TRANSGENIC MOUSE MODEL OF ALZHEIMER'S DISEASE

J. Valla[1,5], K. Chen[1,2,3,5], J.D. Berndt[6], F. Gonzalez-Lima[6], S. Cherry[7], D. Games[8], E.M. Reiman[1,2,4,5]

[1]Harrington Arthritis Research Center, [2]PET Center, Good Samaritan Regional Medical Center, [3]Department of Mathematics, Arizona State University, [4]Department of Psychiatry, University of Arizona, [5]Arizona Alzheimer's Research Center, Phoenix, AZ, USA; [6]Institute for Neuroscience, University of Texas, Austin, TX, USA; [7]Crump Inst for Biological Imaging, Department of Molecular & Medical Pharmacology, UCLA School of Medicine, Los Angeles, CA, USA; and Elan Pharmaceuticals, Inc., San Francisco, CA, USA[8]

Background: Using fluorodeoxyglucose (FDG) positron emission tomography (PET), persons with AD have progressive reductions in posterior cingulate cortex (PCC) activity. Using FDG autoradiography, we found that PDAPP transgenic mice overexpressing a mutant form of the human amyloid precursor protein have progressively reduced activity in the same region, providing a potential brain imaging indicator of AD in these animals.

Objective: To investigate the feasibility of detecting reductions in PCC activity in these mice using non-invasive imaging techniques despite their limited spatial resolution.

Methods: PCC activity was remeasured in the previously studied PDAPP and nontransgenic mice controls after blurring the autoradiographic images to lower spatial resolutions.

Results: The PDAPP mice had abnormally low PCC activity at resolutions of 0.25 and 0.50 mm, no abnormality at 0.75 mm, and abnormally high activity at 1.0 mm. Reversal in the direction of the abnormality appears to be due to effects of a developmentally truncated corpus callosum in PDAPP mice on partial-volume averaging.

Conclusions: While limited-resolution, non-invasive imaging techniques like PET may not be suitable for detecting PCC activity reductions in PDAPP mice, they may still be useful in transgenic mouse lines, such as TG2576 mice, which lack abnormalities in white matter morphology.

(4) EFFECTS OF AGE AND GENE DOSE ON POSTERIOR CINGULATE ACTIVITY IN PDAPP TRANSGENIC MICE

J. Valla[1,7], E.M. Reiman[1,2,3,7], F. Gonzalez-Lima[4], A. Uecker[1], J.D. Berndt[4,5], K. Chen[1,2,7], D. Minear[1], N.L. Callaway[4], D. Games[6]

[1]Harrington Arthritis Research Center, [2]The Positron Emission Tomography Center at Good Samaritan Regional Medical Center, [3]The Department of Psychiatry at The University of Arizona, [4]The Department of Psychology and The Institute for Neuroscience at The University of Texas at Austin, [5]The Neuroscience Program at the University of Wisconsin, Madison, [6]Elan Pharmaceuticals, [7]The Arizona Alzheimer's Research Center, Phoenix, AZ, USA

Background: While transgenic mice have great promise in the study of Alzheimer's disease (AD), uncertainties remain about the extent to which they provide a model of the disorder or the best way to characterize disease progression. Using fluorodeoxyglucose (FDG) autoradiography, we found that very old homozygous PDAPP transgenic mice have preferentially and progressively reduced activity in the posterior cingulate cortex (PCC), as in FDG-PET studies of persons with Alzheimer's disease. If 12-month-old *homozygous* PDAPP transgenic mice have a highly significant decline in PCC activity, studies of these mice could be used to screen candidate treatments more rapidly. If *heterozygous* PDAPP transgenic mice have a similar decline in PCC activity, FDG autoradiographic studies could be used in ongoing studies (e.g. of amyloid-β immunization) of this more commonly used mouse line.

Objective: To further characterize the effects of age and AD gene dose on PCC activity in PDAPP mice.

Methods: FDG autoradiography was used to compare regional/whole brain activity in heterozygotic ($n = 27$), homozygotic ($n = 26$), and littermate controls ($n = 40$) at approximately 2, 12, and 18 months of age.

Results: In the homozygous mice, note a significant but more modest reduction in 12-month-old homozygotes. PDAPP transgenic mice *heterozygous* for a mutant form of the human APP gene did not have detectable declines in PCC activity.

Conclusions: As a potential indicator of AD, FDG autoradiographic measurements of PCC activity in *very old* PDAPP transgenic mice *homozygous* for a mutant form of the human APP gene could be used to help clarify disease mechanisms and screen candidate treatments. Further studies are needed

to determine the extent to which these measurements could provide an indicator of AD in other transgenic mouse lines and other potentially suitable laboratory animals.

(5) DIFFUSION CHARACTERISTICS OF WATER IN THE SPINAL CORD OF A TRANSGENIC MOUSE MODEL OF ALS

P.N. Venkatasubramanian, Ph.D., Alice M. Wyrwicz, Ph.D.

Center for MR Research, ENH Research Institute, Evanston, IL, USA

No specific biological markers are available for the diagnosis of the fatal neurodegenerative disease amyotropic lateral sclerosis (ALS). Neurodegeneration that is similar to the human disease has been detected histologically in G93A transgenic mice (Tg) that overexpress mutated human SOD1 enzyme. Using diffusion MR imaging which is sensitive to changes in tissue structure at the cellular level, we measured the apparent diffusion coefficient (ADC) of water in the spinal cord and found region-specific differences in the Tg mouse spinal cord prior to the onset of any clinical symptoms of the disease. High spatial resolution images ($27\,\mu m \times 54\,\mu m \times 500\,\mu m$) of perfusion-fixed lumbar spinal cords from Tg and normal control mice were recorded on a 9.4 T imager. Apparent diffusion coefficients (D) along z- (parallel to cord length) or y-gradient direction (perpendicular to cord length) were calculated for each pixel in the image from 11 b values (0–4000 s/mm^2). Anisotropy index, $AI = D_z/D_y$, was calculated for gray and white matter regions. Water diffusion was highly anisotropic in the normal white matter with high diffusivity along the length of the cord and much less diffusivity in a perpendicular direction ($D_z = 10 - 20 \times D_y$). In the white matter of the cord from 65-day-old Tg mice, AI was markedly lower as a result of smaller D_z and larger D_y relative to controls. Diffusion in the gray matter was not anisotropic in either the normal or Tg spinal cord ($D_z \sim D_y$), but ADCs were higher in Tg mice. Observed diffusion behavior in Tg mice suggests alterations in the microstructure of neuronal cells and in myelinated tissue of their spinal cord. At 65 days of age, when changes in diffusion were detected by MRI, G93A mice did not show clinical symptoms of motor neuron disease. Immunohistochemical methods could detect earliest cellular changes only 82 days, when symptoms of the disease were already manifesting. Thus, quantitative diffusion MR imaging may have diagnostic potential for early detection of ALS in humans.

(6) REGIONAL GRAY MATTER ATROPHY IN FRONTOTEMPORAL DEMENTIA EVALUATED BY VOXEL-BASED MRI MORPHOMETRY

G.E. Alexander[1,8], K. Chen[2,8], H.J. Rice[1,8], E.M. Reiman[2,8], P. Pietrini[3], D.J. Lewis[1,8], M. Porath[1,8], J.S. Krasuski[4], D. Teichberg[4], S.J. Teipel[5], H. Hampel[5], S.I. Rapoport[4], M.B. Schapiro[6], J. Grafman[7]

[1]Arizona State University, Tempe, AZ, [2]Good Samaritan Regional Med Ctr, Phoenix, AZ, [3]University of Pisa, Pisa, Italy, [4]NIA, NIH, Bethesda, MD, [5]Ludwig Maximillian University, Munich, Germany, [6]Children's Hospital Med Ctr, Cincinnati, OH, [7]NINDS, NIH, Bethesda, MD, and [8]The Arizona Alzheimer's Research Center, Phoenix, AZ, USA

Background: Functional neuroimaging studies have consistently shown reductions in cerebral metabolism and blood flow in frontal and anterior temporal brain regions in patients with frontotemporal dementia (FTD) compared to healthy elderly. Few studies, however, have investigated the regional distribution of gray matter atrophy in this form of primary progressive dementia.

Objective: To evaluate regional gray matter atrophy associated with FTD throughout the brain using voxel-based magnetic resonance imaging (MRI) morphometry.

Methods: Twelve patients with a clinical research diagnosis of FTD (mean age $= 64 \pm 10$ years; 3 males and 9 females; mean Mini-Mental State Exam (MMSE) score $= 19.4 \pm 8.6$) were compared to 30 age-matched healthy controls (mean age $= 65 \pm 9$ years; 11 males and 19 females; mean MMSE score $= 29.7 \pm 0.6$) with T_1-weighted volumetric MRI scans. Statistical Parametric Mapping (SPM99) was used, with procedures optimized to remove artifacts related to non-brain tissue, to transform the brain scans into coordinates of a standard brain atlas, to segment them into gray matter images, and to create a statistical significance map of group differences in gray matter concentration.

Results: Compared to the healthy controls, the FTD patients demonstrated extensive reductions in gray matter, including in orbitofrontal, bilateral anterior temporal, anterior cingulate, bilateral medial and lateral frontal, right thalamus, bilateral hippocampal/amygdaloid, and bilateral perisylvian regions ($3.1 \leq z \leq 4.8$).

Conclusions: The results indicate extensive bilateral brain atrophy in FTD that includes frontal and temporal association and limbic cortical regions with relative preservation of posterior temporal, parietal, and occipital association cortices when compared to healthy elderly controls. These findings provide additional support for the use of voxel-based MRI morphometry to help characterize the, in vivo, effects of neurodegenerative diseases, such as FTD, in the brain.

(7) GENERATION OF A SCREENING MATRIX FOR THE EVALUATION OF IN VIVO DIAGNOSTICS FOR ALZHEIMER'S DISEASE

Sarah Almond, Duncan Hiscock, Denis Bouvet, Sue Champion, Michelle Avory, Shirley Pullan, Ian Wilson, Duncan Wynn

Amersham Plc, Amersham, Bucks, UK

Background: Definitive Alzheimer's Disease diagnosis may allow better patient management and appropriate therapeutic intervention.

Aim: A screening matrix has been developed for the assessment of novel radiodiagnostics of Alzheimer's disease. Successful compounds must be able to cross the blood-brain barrier

Methods: In vitro screens were validated using compounds with varying brain uptake. Screens included those that measure lipophilicity ($\log P$), hydrogen bonding ($\delta \log P$) and an tissue culture model of cell permeability (Papp). These were compared to in vivo screens including brain uptake index, in situ brain perfusion and biodistribution.

Amyloid binding assays measuring binding to fibrillar amyloid 1–40 have been developed. These include a saturation assay (K_d generation) and competition assay. ^{125}I-Amyloid 1–40 has been used to validate an animal model of AD involving the injection of fibrillar amyloid 1–40 into rat hippocampus.

Results: The best correlate between an in vitro model and in vivo permeability was between Papp and BUI ($r^2 = 0.7$). Novel and validation compounds were run through both screens and results used to define screening limits for acceptable BBB penetration of 1×10^{-5} cm/s for Papp and 20% for BUI. Of 50 compounds screened, 2 false-positives (i.e. compounds that penetrated in the Papp and not the BUI) and 0 false-negatives were generated. In situ brain perfusion is only of advantage with slow penetrating compounds, or those that show extensive metabolism upon plasma incubation.

Correlations between BUI and $\log P$ and $\mathrm{dlog}\, P$ were poor—$r^2 = 0.15$ and 0.04, respectively. BUI was validated against percentage injected dose in the brain upon biodistribution (%ID). Correlation between BUI and %ID at 2 and 60 min was seen ($r^2 = 0.9$ and 0.7, respectively). A BUI of 20% predicts a %ID of 0.25% at 2 min post-injection.

Amyloid binding assays mean novel compounds can be ranked against gold-standards (such as ^{3}H-thioflavin) or EC_{50} values against known amyloid binders (e.g. Congo red) can be generated. This allows valuable information regarding the amyloid binding sites of novel compounds to be generated. ^{125}I-Amyloid incorporation and immunohistochemistry were used to demonstrate that injection of fibrillar amyloid into rat hippocampus resulted in reproducible deposits of amyloid in the rat brain.

Conclusion: A screening funnel has been developed as follows: Papp, $\log P$, $\mathrm{dlog}\, P$, in vitro amyloid binding > BUI > biodistribution, brain perfusion > biodistribution in animal models.

(8) CEREBRAL ATROPHY IN DEMENTIA WITH LEWY BODIES STUDIED USING VOXEL-BASED MORPHOMETRY

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Cross-sectional MRI studies using a region of interest (ROI) approach have shown cerebral atrophy in both dementia with Lewy bodies (DLB) and Alzheimer's disease (AD) with relative preservation of the medial temporal lobe in DLB. Voxel-based morphometry (VBM) has advantages over ROI studies in allowing unbiased detection of brain changes wherever they occur. We undertook the first study applying VBM to whole brain MRI scans of patients with DLB compared to control subjects and AD.

Structural MRI scans from 25 DLB (75.4 ± 6.8), 30 AD (78.1 ± 5.3) and 25 healthy age-matched controls (76.2 ± 4.7) were acquired on a 1.5 T GE scanner. Processing was performed using SPM99 and involved spatial normalization to a customized template, segmentation into gray matter, white matter and cerebrospinal fluid partitions, the removal of non-brain voxels and modulation which corrects for the effects of volume change during normalization.

We demonstrated significant gray matter volume loss in the insula, superior, middle and inferior temporal gyri and the superior frontal gyrus bilaterally in patients with DLB compared to controls. Comparison of dementia groups confirmed medial temporal lobe atrophy (parahippocampal gyrus, hippocampus and amygdala) was greater in AD compared to DLB.

Compared to controls we found reduction in gray matter volume in the frontal and temporal lobes of patients with DLB. This fits with the global cognitive impairment which characterises the disease. We also report insular cortex atrophy in DLB compared to controls. When compared to AD, VBM analysis showed relative preservation of the hippocampus, parahippocampal gyrus and amygdala. This supports the view that there are clear structural imaging differences between AD and DLB which help understand the different symptom profiles of the two disorders.

(9) EFFECTS OF WHITE MATTER HYPERINTENSITIES AND LACUNES ON ATROPHY OF BRAIN STRUCTURES IN NORMAL ELDERLY AND DEMENTIA

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Background: Despite numerous measurements of brain structures in normal aging and dementia, the extent to which brain ischemia/infarction affects various structures remains undetermined.

Goal: To determine the effects of brain ischemia/infarction (white matter hyperintensities (WMH) and lacunes) on volume of entorhinal cortex (ERC), hippocampus and cortical

gray matter (CGM) in subjects with cognitive normal (CN) and dementia (D).

Method: Fifty-four subjects with CN (age: 76 ± 5 years, MMSE: 29 ± 1) and 62 subjects with dementia (Alzheimer's disease and vascular dementia, age: 77 ± 7 years, MMSE: 20 ± 6) were included. Eight out of 54 subjects with CN and 33 out of 62 subjects with dementia had subcortical lacunes. ERC and hippocampus were manually measured on MR images. CGM, WMH and lacunes were measured with semi-automatic methods. Associations between volume changes and MMSE score were tested with a linear regression model.

Result: In CN, both WMH ($r = -0.67$, $P < 0.01$) and lacunes ($r = -0.67$, $P < 0.01$) were negatively correlated with volume of CGM; however, neither WMH nor lacunes were correlated with volume of ERC or hippocampus. In D, similar to CN, WMH was negatively correlated with volume of CGM ($r = -0.52$, $P < 0.01$), but not with volume of ERC or hippocampus. In contrast to CN, lacunes were not correlated with volume of CGM, ERC or hippocampus in D. Furthermore, in D, both WMH and lacunes were not associated with MMSE score. MMSE score was associated with volume of CGM ($r = 0.26$, $P < 0.05$), but not of ERC and hippocampus in D.

Conclusion: WMH had effects on volume loss in the cortex, but not in limbic structures in both CN and D. Lacunes had effects on cortex only in the subjects with CN. In the subjects with dementia, global cognitive impairment was associated with CGM loss, not WMSH and lacunes. We conclude that WMH and lacunes have significant effects on brain structures in cognitively normal and demented subjects. Therefore, WMH and lacunes are important confounds in any cross-sectional or longitudinal study of brain structure, including treatment trials.

(10) A MULTI-CENTER TRIAL TO EVALUATE THE CLINICAL UTILITY OF FDG-PET

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Background: Large multi-center studies are needed to validate positron emission tomography with fluorodeoxyglucose (FDG-PET) as a biomarker in dementia, but few have been performed because of the rapid evolution of PET technology and lack of standard methods.

Objective: To develop and evaluate procedures for multi-center clinical trials with FDG-PET.

Methods: Three established Alzheimer's disease (AD) Centers agreed to share imaging data to assess the ability of FDG-PET to distinguish AD and frontotemporal dementia (FTD). Existing files were converted to interfile or ADAC format and sent via the Internet to a central site for reconstruction and analysis while still blinded to clinical information. Six raters received standard transaxial and stereotactic surface projection (SSP) images in a fixed format that could be displayed on their personal computers. Statistical maps also were constructed comparing each individual's results with 33 elderly normals. The raters assigned a diagnosis of AD or FTD with their degree of confidence and assessed the presence or absence of regional hypometabolism and asymmetry unaware of clinical data.

Results: FDG PET-scans were processed from 84 patients originally studied in 1984–1998 who subsequently had a postmortem examination. Although images were from seven different scanners with either BGO or NaI detectors, image processing was successful except in cases with a limited field of view that did not permit automated SSP analysis. In about 10%, minor adjustments were needed for SSP to fix imperfect registrations, primarily due to poor image quality. High diagnostic inter-rater reliability was achieved (mean kappa $= 0.74$).

Conclusions: Multi-center trials of FDG-PET using standardized methods are feasible, even using retrospective data. It will be possible in prospective studies using predetermined scanning parameters to further improve the comparability of data.

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(11) ENTORHINAL CORTEX IN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE: A STRUCTURAL MRI STUDY

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Background: There is a lack of consistent association between brain volume and cognitive decline in early Alzheimer's disease (AD) and mild cognitive impairment (MCI). Consequently, volumetric measure of entorhinal cortex (ER), is not a reliable predictor for the progression AD.

Objective: The aim of this study was to identify a structural imaging marker for early diagnosis of dementia. For this purpose volumetric measurements were compared to the magnetization transfer ratio (MTR) in the ER, bilaterally.

Methods: We acquired 1 mm isotropic T_1-weighted and 1.5 mm isotropic MT and MT-baseline images from 20 normal elderly (NE), 24 AD and 35 MCI subjects. Im-

ages were registered into stereotaxic space and mean MTR and volume within the ER was calculated, following manual segmentation. Variations in the collateral sulcus (CS), which forms the medial boundary for the ER cortex, has a profound affect on the volume of the medial temporal cortices. In our analysis, the variation in CS was taken into account by calculating a ratio of the volume of ER and corresponding segment of CS. This procedure corrected for the variation of the ER cortex due to the CS. The results are described as volume (V), corrected volume (CV) and mean MTR.

Results: The main finding was that the V (mm^3) and MTR were significantly ($^*P \leq 0.05$; $^{**}P \leq 0.01$) lower in MCI ($915 \pm 289^*$) and AD ($808 \pm 249^{**}$) compared to NE (1068 ± 258) but there were no significant differences in CV between NE (7.9 ± 2.7), MCI (6.9 ± 2.7) and AD (7.0 ± 2.6). Both MCI ($31.6 \pm 2.6^{**}$) and AD ($31.6 \pm 2.4^{**}$) subjects exhibited significantly low MTR when compared to NE (34.1 ± 2.4).

Conclusion: Discrepancies in ER measures across laboratories may be due to inconsistent ER boundary and not correcting for the CS variability. Using CV, we found no significant difference in ER volume. Changes in MTR seen in absence of CV differences suggests that MTR may be a more reliable measure of sub-clinical changes in the ER. Thus, structural changes related to AD in the morphologically less well-defined cortical areas such as the ER may be better documented using MT ratios.

(12) STATISTICAL PARAMETRIC MAPPING IN PROVEN LEWY BODY VARIANT OF ALZHEIMERS'S DISEASE

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Objectives: Neuropathologists now generally recognize a form of Alzheimer's disease (AD) in which Lewy bodies (LB) are present in various brain tissues. Clinical symptoms may differ from those of traditional AD with a higher incidence of hallucinations, and a higher incidence of depression. This form of AD + LB is distinct from AD + Parkinson's disease. We propose to analyze five histopathologically proven cases of AD+LB using Statistical Parametric Mapping (SPM) of regional cerebral blood flow (RCBF), comparing results obtained in patients (pts.) with AD.

Methods: Using 99mTc HMPAO and a 3-camera scanner, we have studied 254 pts., with possible or probable dementia, of whom 86 have come to autopsy. Of these, five (four males) have a diagnosis AD + LB. Data from their studies have been registered in Talairach space, and processed by SPM in comparison with a group of eight (four males) elderly normal controls in a study approved by our Institutional Review Board.

Results: Comparisons of groups of voxels in the 5 pts. with AD+LB with the studies of eight normal controls show significant RCBF reduction with uncorrected *k* values not only in expected areas such as the temporal and parietal cortices, and in the posterior cingulate cortex, but also in Brodmann areas (B) 18 and 19, with significant values ranging from $P = 0.00025$–0.00005, respectively, showing involvement of the visual association occipital cortex. No significant localization was seen in B 17, the true visual cortex.

Conclusion: SPM analysis of 5 pts. with proven AD + LB shows findings expected in SPM maps in D plus reduced RCBF in the occipital cortex bilaterally which has been shown by Ishii et al. in a group of 14 pts. with AD + LB diagnosed clinically (Neurology 1999:53;413–416). Similar findings have been identified in the occipital cortex of some individuals with major depressive disorder, which may be a feature of LBD, despite the apparent virtual absence of Lewy bodies from the occipital cortex. The cause of this unusual finding needs to be explored.

(13) MULTI-VOXEL OUTER VOLUME SUPPRESSION PROTON SPECTROSCOPY OF THE CEREBRAL CORTEX IN EARLY DEMENTIA OF THE ALZHEIMER TYPE

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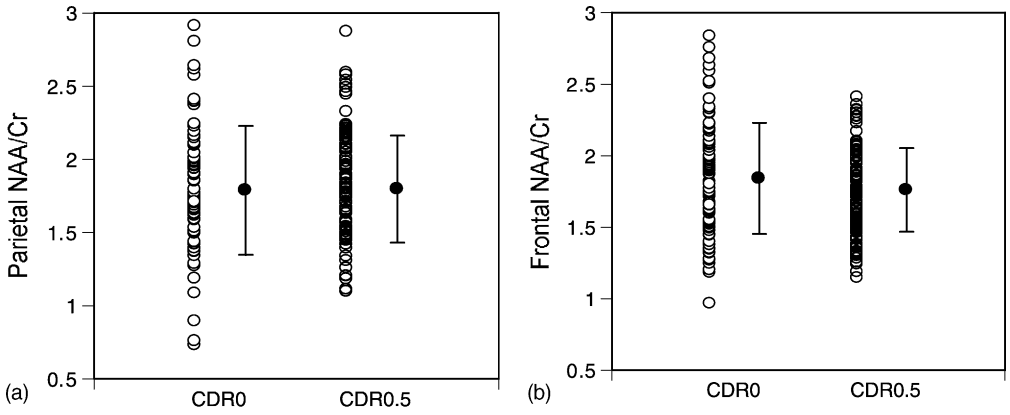
Objective: The objective of this study is to determine the feasibility of detecting early changes of Alzheimer in the cortical gray matter regions using multi-voxel proton spectroscopy.

Materials and methods: Subjects over 65 years of age in the Washington University Human Aging and Senile Dementia population were enrolled in this study based on the Clinical Dementia Rating (CDR) scale and included 30 normal (CDR0) and incipient or early DAT (CDR0.5). The scans will be repeated 2 years after the initial studies. A 2D multi-voxel proton spectroscopy technique utilizing outer volume suppression (OVS) of the skull and scalp was used to interrogate the front and parietal cortical and inter-hemispheric gray matter. The scan was placed at the level of the cingulated gyrus parallel to the AC–PC line using spin-echo technique (TR1500, TE135 with 64 voxels each $1.5\,cm^3$). The relevant voxels of the gray matter in the frontal and parietal regions were processed with manual phase, baseline correction and Gaussian fitting of the integra of the *N*-acetylasparate, creatine and choline regions. Strict criteria for spectral line-with and homogeneity were applied for selection of voxels to be included for analysis. The spectra of 44 subjects processed comprised 100 frontal, 78 parietal voxels (19 CDR0), and 125 frontal, 100 parietal voxels (22 CDR0.5). The spectra in three subjects were suboptimal. The ratios of NAA/Cr and NAA/Cho + Cr in the gray matter were compared and statistically analyzed.



CDR0.5, mean = 1.71, SD = 0.29 CDR0.5, mean = 1.80, SD = 0.37
CDR0, mean = 1.84, SD = 0.39 CDR0, mean =1.79 , SD = 0.44
Independent samples t-test, P=0.006 Independent samples t-test, p=0.87

Fig. 1.

Results: The NAA/Cr and NAA/Cr + Cho in the frontal voxels of the summed CDR0 had a mean value 0.13 higher than CDR0.5 subjects $P < 0.006$ (Fig. 1a). The results of the frontal gray matter show promise but cannot be used for early diagnosis of DATA in individual cases because of the overlap of the data between the groups. The difference in the parietal gray matter is not statistically significant (Fig. 1b). Analysis of the spectra between individual CDR0.5 and normal subjects and the significance in diagnosing DAT will be presented.

(14) DEVELOPMENT OF THIOFLAVIN-T ANALOGS FOR AMYLOID IMAGING WITH PET

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Objectives: Synthesize and evaluate the properties of ^{11}C- and ^{18}F-labeled analogs of thioflavin-T (ThT) as potential in vivo tracers of amyloid in Alzheimer's disease (AD) for use with positron emission tomography (PET) imaging.

Methods: Approximately 100 analogs of ThT were synthesized, and their binding affinities for β-amyloid fibrils (Aβ1–40) were determined. About 30 of these analogs were radiolabeled with high specific activity ^{11}C or ^{18}F, and their in vitro and in vivo properties were evaluated.

Results: The estimated $\log(P_{\text{oct-water}})$ values of the radiolabeled analogs varied from 1.5 to 4.0, spanning the optimum range for good brain uptake. The binding affinities of the radiolabeled analogs for Aβ1–40 varied from 1 to 60 nM, with ca. 10 of the most promising compounds exhibiting values <10 nM. Brain uptake of these analogs in normal mice post i.v. tail–vein injection varied from 8 to 18%ID/g at 2 min to 0.8–4%ID/g at 30 min, indicating excellent brain penetration and good clearance of free and non-specifically bound tracer from brain. PET studies in normal baboons provided similar brain uptake (%ID-kg/g) values. Plasma samples from mice and baboons indicated rapid metabolism of all analogs, with <10% parent compound remaining 60 min post-injection and the absence of radiolabeled lipophilic metabolites. Binding studies using postmortem brain tissue homogenates resulted in specific binding ratios in AD cortical brain relative both to cerebellar and to age-matched control cortical brain of 3:1 to >20:1. Scatchard analyses indicated that the high affinity binding component of the analogs was unique to AD cortical brain, with K_d values ranging from 1 to 15 nM and Bmax values from 5 to 20 pmol/mg wet wt. (∼5–20 μM).

Conclusions: The in vitro and in vivo properties of ^{11}C- and ^{18}F-labeled analogs of ThT provide several promising amyloid imaging agents for PET. In vivo PET imaging studies in transgenic mice and AD subjects with several of these compounds are currently underway.

(15) EVALUATION OF A POTENT THIOFLAVIN-T ANALOG FOR IN VIVO IMAGING OF AMYLOID WITH PET

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Objectives: Evaluate the properties of a ^{11}C-labeled analog of thioflavin-T (ThT) as a potential in vivo marker of amyloid in AD for use with PET imaging.

Methods: More than 100 analogs of ThT were synthesized, and their in vitro and in vivo properties were evaluated in an effort to identify a promising tracer for in vivo brain imaging studies of amyloid deposition.

Results: A lead compound, termed 6-OH-BTA-1 (2-[(4′-methylamino)phenyl]-6-hydroxybenzothiazole), was selected based upon several properties. The binding affinity (K_d) of [^{11}C]6-OH-BTA-1 for β-amyloid (1–40) fibrils was 2 nM. The estimated log($P_{oct\text{-}water}$) value of 6-OH-BTA-1 was 1.6, in the range predicted for good brain uptake. The brain concentration of [^{11}C]6-OH-BTA-1 in normal mice post i.v. tail–vein injection was 9.5%ID/g (0.24%ID-kg/g) at 2 min and 0.8%ID/g (0.02%ID-kg/g) at 30 min, indicating good brain uptake and clearance of free and non-specifically bound tracer. PET studies in normal baboons provided similar brain uptake values (0.22%ID-kg/g at 5 min) and somewhat slower clearance rates (0.05%ID-kg/g at 60 min). Plasma samples from mice and baboons indicated rapid metabolism of [^{11}C]6-OH-BTA-1, with ∼80% parent compound at 2 min and <10% at 30 min post-injection. Plasma from mice and baboons did not contain radiolabeled, lipophilic metabolites of [^{11}C]6-OH-BTA-1, and radiolabeled metabolites were absent in the excised brains of mice. In binding studies using postmortem brain tissue homogenates, specific binding ratios in AD cortical brain relative both to cerebellar and to age-matched control cortical brain were >20:1. Scatchard analyses indicated that [^{11}C]6-OH-BTA-1 specific binding was unique to AD cortical brains, fit a single site model, and demonstrated K_d values of 6–9 nM and B_{max} values in of 7–10 pmol/mg wet wt. (∼7–10 μM).

Conclusions: The in vitro and in vivo properties of [^{11}C]6-OH-BTA-1 make it a promising amyloid imaging agent for studies in transgenic mice and AD subjects.

(16) THE HIPPOCAMPUS: FROM QUALITATIVE ASSESSMENT, LINEAR MEASURE, MANUAL SEGMENTATION, AUTOMATED VOLUMETRICS, AND TENSOR MAPPING

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Objective: We demonstrate our experience with a spectrum of classical assessment techniques of the hippocampus in normal aging, mild cognitive impairment (MCI), and Alzheimer's disease (AD) in over 100 cross-sectional and longitudinal MRI scans compared to results obtained from a fully automated stochastic sub-volume probabilistic AD atlas (AD-SVPA) and semi-automated continuum-mechanical 3D surface mapping approach.

Background: Recent developments in human brain mapping have instigated the extension of average deterministic anatomic brain atlases to a new class of probabilistic sub-volume population specific atlases. Aging and dementing diseases impose the most extreme changes on brain structure and function making existing atlases inappropriate for use in these populations. Disease specific Atlases overcome this structural mismatch. After construction of a continuum mechanical average population brain atlas, with manually partitioned regions of interest encoding anatomic and registration variability, rates of WM, GM, and CSF volume change over time can be determined in an automated method.

Methods: High resolution SPGR MRIs of 103 subjects with normal aging, MCI, and AD were registered to the UCLA-AD Atlas via linear and non-linear transforms. Qualitative, linear, volumetric, and 3D surface mapping was conducted and compared across examiners, and techniques.

Results: The relationships among classical approaches, as well as a fully automated atlas-based approach, to measuring the hippocampus are compared with 3D morphologic maps that localize surface *r*-values with hippocampal population-based shape changes across the three groups.

Conclusion: An automated, unbiased, hippocampal surface extraction technique shows promise in assessing medial temporal atrophy in MCI, and AD. Overall, past classical assessment techniques show the best correlation with 3D surface mapping at the hippocampal head.

(17) NEUROPATHOLOGICAL CORRELATES OF BRAIN MRI IN THE FRAMINGHAM HEART STUDY

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Objective: To identify the neuropathological correlates of quantitative MRI findings in a community-based population.

Background: Numerous MRI studies have documented differences in brain structure across the span of human aging and in the presence of disease. Principal to this research is the assumption that in vivo brain imaging reflects true pathological processes. While this assumption is considered generally valid, there is only limited information comparing quantitative MRI measures of regional brain structure to post-mortem neuropathological findings. To examine these relations, we performed rapid post-mortem MRI on 11 consecutive individuals from the Framingham Heart Study (FHS) and compared regional brain volumes to various neuropathological findings.

Design/methods: The FHS is a longitudinal cohort study designed to examine the epidemiology of cardiovascular disease in a defined community population. The current FHS cohort includes the original members and their offspring. Participating individuals are asked to consent to autopsy that includes rapid MRI imaging of post-mortem brain within 24 h of death whenever possible. For this study, 11 individuals were imaged using a conventional coronal double-echo MR protocol (TR2400, TE20/80) and quantified according to previously reported methods. Neuropathological assessment included ascertainment of brain weight

and semi-quantitative estimates of cerebral atherosclerosis, stroke and Alzheimer's disease (AD) pathology. Simple correlation and stepwise regression analyses were used to estimate the relationships between regional brain volumes and neuropathological findings.

Results: Individuals were 80.4 ± 12.5 years of age on average at the time of death (range 66–99). Using NIA-Regan criteria, three individuals had high likelihood of AD, two had intermediate likelihood and the remaining six individuals had low to no likelihood of AD. All individuals with NIA-Regan criteria of high likelihood were clinically demented. Cerebral infarcts greater than 1 cm in diameter were present in three individuals, less than 1 cm in one additional individual and microscopic infarcts were present in two others. This spectrum of pathology allowed us to categorize subjects into four groups: Normal, AD, CVD and Mixed. Subjects with AD had significantly small brain weights (mean 1125 g) and brain volume (mean 709 ml) as compared to normals (1252 g and 870 ml, respectively). The temporal pole of the lateral ventricle was significantly enlarged as compared to normal (0.56 ml versus 0.09 ml). For subjects with CVD, brain weight and brain volume were nearly identical to normal (1277 g and 892 ml), but the volume of white matter hyperintensities (WMH) was significantly increased (23.4 ml versus 3.0 ml). Brain weight was significantly correlated with MRI brain volume ($r = 0.96$, $P < 0.0001$) and Braak and Braak score ($r = -0.35$, $P < 0.05$). WMH correlated significantly with number of microscopic infarcts.

Conclusions: MRI measures of cerebral size are reasonably accurate estimates of true brain size. In addition, AD pathology was associated with generalized brain atrophy and enlargement of the temporal horn of the lateral ventricle whereas CVD pathology was associated with WMH volume. We conclude the in vivo MRI estimates are good correlates of AD and CVD pathology in this small sample.

(18) CRITICAL REVIEW OF THE NINDS–AIRENS VASCULAR DEMENTIA CRITERIA

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The NINDS–AIREN International Workshop met in 1991 and published their diagnostic criteria on vascular dementia (VaD) in 1993. Over the last 5 years there has been considerable interest in testing new treatments for VaD and a number of large-scale placebo-controlled trials have been completed or are in progress using these criteria as the "gold standard" for eligibility.

The diagnostic criteria for probable vascular dementia include the development of dementia temporally related to stroke, with imaging confirmation. The criteria include a table listing brain imaging lesions associated with vascular dementia. Some of the problems with this list include; lack of clinicopathological validation, exclusion of lesions that may produce dementia such as unilateral strategic thalamic infarctions and unilateral anterior cerebral artery infarctions, and inclusion of criteria that are hard to measure such as leukoencephalopathy involving 25% of the white matter and lack of specificity about the number of frontal and subcortical basal ganglia lacunes required The criteria lack a clear definition of slowly progressive forms of VaD such as CADASIL and Binswanger's disease. The criteria also require memory loss and two other areas of cognitive impairment plus evidence of neurological signs, even though memory loss and neurological signs may not be prominent features.

In the original report the authors state that the criteria require validation and should be revised as more information becomes available. Given the widespread interest in developing therapeutic interventions for VaD and the need to differentiate VaD from Alzheimer's disease and other forms of dementia, the time is right for a critical review and revision of the NINDS–AIREN criteria. The imaging characteristics of VaD subjects from recent clinical trials using these criteria will be presented to highlight the main strengths and limitations of the current criteria and suggestions for revision will be offered.

(19) REGIONAL REDUCTIONS OF BLOOD FLOW IN CORTEX AND WHITE MATTER IN ALZHEIMER'S DISEASE

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Background: Previous PET and SPECT studies have shown reduced cerebral blood flow (CBF) and metabolism in AD, presumably due to diminished function caused by disconnections between neurons.

Objectives: (1) To measure regional variations of CBF in gray matter and white matter of AD and normal aging using arterial spin labeled MRI; (2) To determine the extent to which CBF, together with structural MRI classifies AD from normal aging.

Method: Thirteen AD patients (age: 73.8 ± 4.9 years; MMSE: 23.0 ± 5.9) and 17 cognitively normal subjects (age: 73.4 ± 8.2 years; MMSE: 29.6 ± 0.5) had CBF measured using pulsed arterial spin labeled perfusion MRI and volumes of hippocampus, cortical gray matter (GM) and white matter (WM) of the main lobes determined using high resolution MRI. CBF was corrected for partial volume and tissue type (GM, WM, and CSF) by coregistering the perfusion MRI with structural MRI.

Results: Compared to controls, AD had 27–30% lower CBF ($P < 0.001$ by MANOVA) in GM of both the frontal and the parietal lobes and 24% lower CBF ($P < 0.01$) in GM of

the temporal lobe. Furthermore, these CBF reductions were correlated with severity of impairment. In frontal lobe GM of AD, CBF was significantly lower on the left than on the right side, in contrast to controls, who showed no asymmetry. CBF was also reduced in WM of AD compared to controls by about 20% ($P < 0.01$). Hippocampal size alone correctly classified AD from controls with 84% sensitivity and 82% specificity for AD. Frontal gray matter CBF correctly classified AD with 85% sensitivity and 94% specificity. This is similar to previous reports of AD using PET. The two measures taken together achieved an overall correct classification of 93 and 92% sensitivity and 94% specificity for AD.

Conclusion: Reduced CBF in gray and white matter of AD suggests dysfunctions in both tissue types. Furthermore, the improvement in discriminating AD patients from controls using CBF and structural changes together implies that each make independent contributions to the characterization of AD and normal aging.

(20) DETECTION OF ALZHEIMER'S AMYLOID LESIONS IN TRANSGENIC MICE BY MAGNETIC RESONANCE IMAGING

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A number of potential therapeutic approaches have been developed for the in vivo clearance of amyloid-β (Aβ) lesions, which characterize Alzheimer's disease (AD). However, currently the definitive diagnosis of AD requires post-mortem examination. We present a novel method for the detection of Aβ plaques by magnetic resonance micro-imaging (MRI) using transgenic mouse models of AD. This method utilizes Aβ1–40 peptides, which are labeled with either gadolinium (Gd) or monocrystalline iron oxide nanoparticles (MION). When either of these ligands is injected in vivo systemically with mannitol to transiently open the blood-brain barrier, we are able to image the majority of Aβ plaques in the extracted intact brains. Using Gd labeled Aβ1–40 and in vivo MRI, we are also able to detect a substantial percentage of amyloid lesions. This approach can be used to monitor potential therapeutic amyloid clearance in AD model mice in vivo and with further development could be the basis for plaque detection in AD patients.

(21) BIOLOGICAL CORRELATES TO CLINICAL SUBGROUPS OF ALZHEIMER'S DISEASE

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Background: The presence of clinical subgroups of Alzheimer's disease (AD) based on prevailing symptomatologic features has previously been suggested. One of these subgroups, AD type I (ADI), is characterized by the presence of a predominating parietal brain regional syndrome and another, AD type II (ADII), by a more global syndrome. These symptomatological differences may have biological correlates such as different metabolic profiles.

Objective: To investigate underlying biological correlates to clinical subgroups of AD.

Method: We investigated the regional cerebral blood flow (rCBF) using single photon emission tomography (SPECT; technetium-HMPAO), and the cerebrospinal fluid (CSF) levels of the monoamine metabolites in 15 patients with ADI, 36 with ADII, and also in 16 with frontotemporal dementia (FTD) and in a control group. The investigations were performed within 4 days in most cases. Differences in age, gender ApoE4 allele inheritance and degree of cognitive impairment were taken into account.

Results: In general, rCBF in parietotemporal cortical regions were found to be decreased in both ADI and ADII compared to controls ($P < 0.001$). However, some changes were found only in ADII such as decreased rCBF in the hippocampus ($P < 0.01$, bilaterally), the frontal white matter ($P < 0.01$, bilaterally) and the left frontal association area ($P < 0.05$). Decreased rCBF in frontal regions characterized FTD. Regarding the monoamine metabolite levels, CSF-HVA was decreased only in ADI ($P < 0.001$), but CSF-5-HIAA and CSF-HMPG was decreased in both ADI and ADII ($P < 0.05$ for all). Correlations between CSF-HVA and rCBF were found in several cortical regions only in ADI.

Conclusion: The results suggest the presence of underlying biological correlates to the phenomenological discrepancies between ADI and ADII.

(22) NETWORKS MEDIATING COGNITIVE RESERVE IN NORMAL AGING AND AD

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Higher levels of education and IQ have been associated increased cognitive reserve against the clinical expression of AD, but the mechanism underlying this protective effect is unknown. We explored the relationship between indices of reserve and expression of specific brain networks activated during the performance of a non-verbal serial recognition test in 17 healthy elders and 10 AD patients. A cognitive reserve factor score (CRF) summarized three variables: New Adult Reading Test estimated IQ (NART), WAIS-R Vocabulary (Voc), and years of education (Educ). The activation test had two conditions: *low demand*, with a study list size of one; and *titrated demand*, where the study list size was pre-determined for each subject to elicit a recognition accuracy of 75%. We used Scaled Subprofile Modeling (a PCA-based, multivariate analytic method) to identify two topographies (or brain networks): one that was commonly expressed by old and AD subjects (i.e. the mean change in expression of this topography across the two conditions was comparable in the two groups), and a second that was differentially expressed by the two groups.

The common topography consisted of increased activation in right lingual gyrus, and calcarine and parietal (inferior and superior) cortex, and decreased activation in anterior insula and thalamus. In the elders, expression of this topography correlated positively with Educ and CRF; in AD it correlated with NART and CRF. These consistent correlations with reserve variables suggests that this manifestation of reserve is present in normal aging and is preserved in the AD patient.

In the elders, the differentially expressed topography took the form of increased expression of right hippocampus coupled with decreased expression of association cortex; AD patients showed the opposite pattern. Relative expression of the differential topography did not correlate with reserve variables in the elders. In the AD patients there was a positive correlation between Educ, NART, Voc, and CRF and the expression of their pattern, suggesting that differential utilization of this topography by AD patients represents a compensatory mechanism.

Two separate neural substrates of cognitive reserve were noted: one reflecting differential inherent ability, observed in both normal aging and AD; and one reflecting differential ability to compensate for the effects of pathology, noted in AD only.

(23) VOXEL-BASED MORPHOMETRY OF THE MEDIAL TEMPORAL LOBE: VALIDATION STUDY

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Background: Region of interest (ROI)-based measurements of atrophy of medial temporal lobe (MTL) structures are sensitive markers of AD, but some overlap may exist with non-demented controls.

Objective: To test whether voxel-based morphometry with Statistical Parametric Mapping (SPM) can detect atrophy in AD patients and controls overlapping on MTL ROI-based volumetric measures.

Methods: Overlapping cases were taken from 27 probable AD (MMSE: 12–27) and 25 non-demented controls who had undergone high resolution 3D brain MR and ROI-based measurements of hippocampal and entorhinal cortex volumes. When the distribution of volumes was plotted against age, eight AD patients and five controls were overlapping by hippocampal (1524 ± 237 and $1541 \pm 158\,\mathrm{mm}^3$; $P = 0.88$) and 15 and 10 by entorhinal cortex measures (869 ± 135 and $891 \pm 116\,\mathrm{mm}^3$; $P = 0.67$). MR images were processed using SPM procedures: spatial normalization of the whole brain to a stereotactic template, segmentation of images into gray matter, white matter and cerebro-spinal fluid, and smoothing of the gray matter. Analyses were carried out with $P < 0.05$ uncorrected, and age and sex were included as covariates.

Results: The test of atrophic regions of overlapping AD compared to overlapping controls showed bilateral atrophy in the MTL region. Large clusters of atrophy (measuring 52–53 ml on the right and 15–22 ml on the left side) were detected including MTL and temporo-parietal regions. Peaks of atrophy were in the MTL (tail of the right hippocampus and head of the left hippocampus) and outside the MTL (right insula, middle frontal, and superior temporal gyri, and left inferior temporal gyrus). On the contrary, the test of atrophy in controls compared to AD resulted in small (9–14 ml) areas located in the occipital lobe.

Conclusions: In AD patients whose MTL volumes are normal by conventional measures, SPM can detect atrophy within and outside the MTL. Voxel-by-voxel detection of atrophy is a sensitive marker of AD.

(24) AN ON-LINE ARCHIVE OF HIGH-CONTRAST STRUCTURAL DATA FROM 300+ DEMENTED AND NON-DEMENTED PARTICIPANTS

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Background: Automated, quantitative assessment of anatomy may allow measurements of subtle structural change to predict dementia, monitor its progress, and differentially diagnose subtypes of dementia.

Objective and method: To facilitate such research, data were collected on 300+ participants across the lifespan (age: 18–93 years), with the majority being 65 years of age or older and 71 participants, age 80 years or older. Older adults were enrolled as demented or non-demented based on a Clinical Dementia Rating (CDR) scale with follow-up assessments occurring at 1–2 years at the Washington University Alzheimer's Disease Research Center. Subsets of subjects were enrolled with uncommon diagnoses including semantic and non-fluent subtypes of progressive aphasia. Participants were imaged using three or more high-resolution MP-RAGE T_1-weighted sequences optimal for gray-white tissue contrast. Advanced imaging protocols were also collected on some participants (e.g. diffusion tensor imaging 100+ participants; hippocampal-optimized FLASH sequences on 200+) and 51 having follow-up scans.

Results: A large structural data set with high contrast-to-noise properties for automated, computational anatomic approaches was produced. Network-based computational procedures were deployed to automate analysis, and a Web-based visualization tool was built to provide broad access to the database.

Conclusions: The repository and its associated tools demonstrate an approach that allows for large-scale data mining of structural data sets as well as the feasibility of fully automated network-based computational analysis. This available on-line data set has provided support for a broad range of clinical and basic science studies.

(25) ENTHORINAL CORTEX ATROPHY IN POST TRAUMATIC STRESS DISORDER

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Background: Entorhinal cortex (ERC) is thought to be an early site in the development of Alzheimer's disease (AD). Some studies have suggested that MRI-measured ERC volumes are a good predictor of future AD. Furthermore, stress and high cortisol levels may damage median temporal lobe structures.

Objective: To determine the extent to which post-traumatic stress disorder (PTSD) and cortisol levels affect the rate of ERC atrophy.

Methods: Nine PTSD patients (54 ± 3 years) and nine normal participants (55 ± 6 years) had volumetric T_1-weighted MRI scans (MPRAGE, TR/TI/TE = 10/300/4 ms) twice 2.6 ± 0.5 years apart. An experienced rater traced the ERC on both sides manually. Salivary cortisol measurements were obtained before and after a Dexamethasone (0.5 mg) challenge at the time of the baseline MRI.

Results: ERC volumes at both time points did not differ between groups ($P > 0.4$ by t-test). PTSD had a greater percentage annual loss of ERC volume than controls ($F(2, 15) = 5.1$, $P = 0.02$ by MANOVA, covaried for age). This effect was mainly driven by the left ERC (annualized loss: $1.1 \pm 0.6\%$ in PTSD versus $0.0 \pm 0.8\%$ in controls; $F(2, 15) = 10.8$, $P = 0.005$), with no group difference in the right ERC atrophy rate ($0.7 \pm 1.8\%$ in PTSD versus $0.4 \pm 1.3\%$ in controls, $F(2, 15) = 0.1$, $P = 0.7$). Salivary cortisol levels were not significantly different between groups. Furthermore, cortisol levels did not correlate significantly with ERC atrophy rates. However, baseline cortisol levels (pre-Dexamethasone) in PTSD patients correlated with left ERC volume at baseline ($r = 0.93$, $P = 0.003$ by Pearson) and at follow-up (both $r > 0.93$, $P < 0.003$). The corresponding correlations were not observed in controls (both $r = 0.04$, $P = 0.8$).

Conclusion: These preliminary results show an association between cortisol levels and ERC volume in PTSD patients and a greater ERC atrophy rate in PTSD compared to cognitively normal controls. Because AD pathology begins in the ERC, the results suggest that PTSD may be a risk factor for AD.

(26) HIPPOCAMPAL VOLUME PREDICTS DEMENTIA-FREE SURVIVAL UP TO TWELVE YEARS BEFORE SYMPTOM ONSET

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Objective: To examine whether hippocampal volume along with other putative risk factors for dementia predict timing of future cognitive decline.

Background: Few biological markers predict the onset of sporadically occurring Alzheimer's disease (AD) years prior to cognitive decline. Brain regions such as hippocampus, known to presymptomatically harbor the neuropathology of AD, may show volume loss years before onset of clinical dementia symptoms and thus serve as a predictive biomarker.

Methods: One hundred and seventeen healthy cognitively intact men and women (mean age = 84.0 ± 7.4 S.D.) were followed prospectively at 6-month intervals for up to 12.6 years (mean years = 7.3 ± 2.9 S.D.) and evaluated for incident cognitive decline. All subjects scored CDR = 0 at entry. Brain MRI obtained at entry into the study was quantitatively analyzed for hippocampal and intracranial volume (ICV).

Results: During the observation period, the incidence of cognitive decline, defined by the CDR, was 59% (68/117). In univariate analyses examining putative risk factors for

dementia, the group developing cognitive impairment did not differ from the group remaining intact in gender, years of education, family history of memory impairment, or MMSE at entry. The groups did differ in age, hippocampal volume, presence of the apolipoprotein E-4 allele (ApoE-4), and intracranial volume (a measure of constitutional brain size). In a Cox proportional hazards model, survival free of dementia was significantly predicted by hippocampal volume at entry ($P = 0.0001$), age at entry ($P = 0.0023$), and the presence of the ApoE-4 allele ($P = 0.0482$). ICV was not a significant factor in this model ($P = 0.1659$). The magnitude of risk for developing cognitive impairment within a mean of 5 years for the following factors was: hippocampal volume (per additional 0.1 ml) reduced risk by 27.5% (CI: 14.5–38.6%); age (per additional year) increased risk by 7.1% (CI: 2.5–11.9%); ApoE-4 (presence of at least one allele) increased risk by 75.4% (CI: 0.4–206.2%).

Conclusion: Hippocampal volume is a strong factor independently predicting dementia-free survival. Combined with other known risk factors, high-risk individuals even among healthy elderly can be identified years before symptoms emerge. Identification of these individuals may be key in studies of dementia prevention and treatment.

(27) ORBITAL FRONTAL AGING: EVIDENCE FOR EARLY DETECTION OF COGNITIVE CHANGES USING FMRI

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Background: Prefrontal cortex is among the brain areas most sensitive to age-related volume loss but characterization of whether changes are region-specific or involve the entire prefrontal cortex has received little attention.

Objective: Based on our observations of orbital frontal cortex (OFC) vulnerability to age-related volume loss, we investigated age differences in OFC function.

Methods: fMRI was performed during delayed match and nonmatch to sample tasks, previously shown to selectively activate medial and lateral OFC, respectively, in young adults. Healthy volunteers (10 men/10 women) were divided into equal-sized cohorts of younger (20–40 years; mean = 29.2 ± 6.9) and older (60–80 years; mean = 67.1 ± 4.6) adults. Groups did not differ on overall cognitive status (MMSE: young = 29.6 ± 0.7, elderly = 29.1 ± 1.5), education or depressive symptoms. Brain EPI images were acquired on a Phillips 1.5 T system using an event-related design. Participants chose the stimulus from a pair of stimuli matching a previously viewed target (*match* to sample) or chose the non-target item (*nonmatch* to sample) depending upon a trial-specific instruction word.

Results: SPM99 analyses revealed greater activation for medial OFC regions during the match task compared to the nonmatch task and greater lateral OFC activation during the nonmatch task compared to the match task. Once divided by age, younger participants continued to show the medial OFC/match and lateral OFC/nonmatch pattern. In contrast, older adults showed less prefrontal activation during the match task and more diffuse prefrontal involvement during the nonmatch task.

Conclusion: This study is the first to assess functional correlates of specific regions of structural loss in OFC in the elderly. Results suggest differential age-related recruitment of prefrontal regions when performing OFC tasks. As OFC regions show early evidence of amyloid deposition in aging and Alzheimer's disease, activation patterns during OFC tasks may mark an avenue of research into predicting cognitive decline.

(28) CONSIDERING THE VARIABILITY OF THE COLLATERAL SULCUS IN THE SEGMENTATION OF PARAHIPPOCAMPAL CORTEX STRUCTURES FROM MR IMAGES

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The medial temporal lobe (MTL) is discussed as being affected early in the course of Alzheimer and other neurodegenerative diseases, and could thus potentially serve as a diagnostic marker. However, volumetric analysis of the entorhinal cortex and other MTL structures has so far failed to establish these measures as reliable predictor for Alzheimer or other diseases. The current segmentation protocol was developed to investigate whether the introduction of a correction method for the variability of the collateral sulcus can benefit the amount of information derived from MTL measurements.

A total of 40 MR images (20 men and 20 women, age range: 18–42 years) were employed. Data were registered into standard stereotaxic space, and volumetric analysis was performed manually using in-house 3D software. Intra- and inter-rater correlation coefficients were high ($r = 0.85$–0.96). After correction of the different cortices of the parahippocampal gyrus for the variability of the collateral sulcus, a negative correlation with age appeared for part of the parahippocampal gyrus in the group of men but not women.

The results confirmed previous findings of manual segmentation of medial temporal lobe structures, with comparable mean volumes as well as coefficients of variation.

It was intriguing to see a negative correlation with age appear for part of the MTL in men after the correction for the variability of the collateral sulcus was applied. This suggests that this method might potentially add important information about the association of specific MTL structures with other variables. Future studies will have to establish whether this correction method will also be useful as predictive marker for specific neurodegenerative diseases.

(29) EFFECTS OF AGE ON CEREBRAL GLUCOSE METABOLISM IN CARRIERS AND NONCARRIERS OF THE APOLIPOPROTEIN E ε4 ALLELE: A POSITRON EMISSION TOMOGRAPY STUDY IN YOUNGER AND OLDER ADULTS

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Objective: To investigate the effects of age on cerebral glucose metabolism (CMRgl) in cognitively normal carriers and noncarriers of the apolipoprotein E ε4 allele.

METHODS: Fluorodeoxyglucose positron emission tomography was performed in 12 ε4 carriers and 15 noncarriers 31 ± 5 years of age and 13 ε4 carriers and 12 noncarriers 71 ± 5 years of age. The carriers had the ε3/ε4 genotype; 12 noncarriers in each age group were individually matched to carriers for gender, age and educational level. A brain-mapping algorithm was used to normalize data for absolute measurements and generate surface-projection *t*-score maps ($P < 0.001$, uncorrected for multiple comparisons).

Results: In comparison with ε4 noncarriers in the same age range, the younger ε4 carriers had abnormally low CMRgl in each of the same posterior cingulate, parietal, temporal, and prefrontal regions as patients with probable AD and in additional parietal, temporal, and prefrontal regions; surprisingly, the older cognitively normal ε4 carriers did not, raising the possibility that a proportion of older ε4 carriers vulnerable to AD did not meet our strict cognitive normality criterion due to initial cognitive decline. In comparison with their younger counterparts, the older ε4 carriers and noncarriers each had lower CMRgl in the whole brain (in mg/min/100 g, $P < 0.06$), and lower regional/whole brain ratios in extensive areas of the medial prefrontal and anterior cingulate cortex and discrete areas of lateral frontal, parietal and temporal cortex.

Conclusions: This study demonstrates functional brain abnormalities in relatively young adult APOE ε4 carriers; it provides information about the cerebral metabolic correlates of normal aging; and it suggests that our "cognitive normality" criterion should be liberalized when APOE ε4 carriers over the age of 65 are included in preclinical studies of AD.

(30) ABNORMALITIES IN REGIONAL BRAIN ACTIVITY IN YOUNG ADULTS AT GENETIC RISK FOR LATE-ONSET ALZHEIMER'S DISEASE

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Background: Using fluorodeoxyglucose (FDG) positron emission tomography (PET), we previously found that 50–65-year-old cognitively normal carriers of the apolipoprotein E (APOE) ε4 allele, a common susceptibility gene for late-onset Alzheimer's disease (AD), had abnormally low activity in the same brain regions as patients with probable AD.

Objective: To detect functional brain abnormalities in relatively young adults at genetic risk for late-onset AD.

Methods: Twelve APOE ε4 carriers 31 ± 5 years of age (all with the ε3/ε4 genotype) and 15 ε4 noncarriers 31 ± 5 years of age (12 of whom were individually matched to each of the ε4 carriers) had a neurological exam, a structured psychiatric evaluation, dementia and depression ratings, neuropsychological tests, volumetric magnetic resonance imaging, and FDG-PET as they rested quietly with their eyes closed. An automated algorithm was used to normalize images for the variation in pontine measurements, generate a three-dimensional stereotactic surface-projection *t*-score map of significant differences in regional brain activity, and compare it to a map previously generated from patients with probable AD and their own normal controls.

Results: The young adult APOE ε4 carriers and noncarriers did not differ significantly in their age, gender distribution, educational level, dementia or depressive ratings or neuropsychological test scores. The ε4 carriers had abnormally low brain activity bilaterally in each of the same posterior cingulate, parietal, temporal, and prefrontal regions as patients with probable AD and in additional parietal, temporal, and prefrontal regions ($P < 0.001$, uncorrected for multiple comparisons).

Conclusion: Carriers of a common susceptibility gene for late-onset AD have characteristic abnormalities in regional brain activity in relatively young adulthood, several decades prior to the possible onset of dementia.

(31) FAMILIAL ALZHEIMER'S DISEASE: HOW EARLY DOES MEDIAL TEMPORAL LOBE ATROPHY OCCUR?

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Background and aims: In this study we assessed global and regional brain volumes and atrophy rates in patients with familial Alzheimer's disease (AD) over the period they developed symptoms. By extrapolation, we estimated how

long regional atrophy was occurring prior to the onset of symptoms.

Methods: Five patients with pre-symptomatic AD and 20 age-matched controls had two or more annual T_1-weighted volumetric MR brain scans. Volumes of whole brain, ventricles, temporal lobes, hippocampi and entorhinal cortices (EC) were measured and corrected for total intracranial volume. Rates of atrophy were calculated from the serial scans; rates of whole brain atrophy were also calculated using the brain boundary shift integral. Baseline volumes and atrophy rates in cases and controls were used to extrapolate to points of divergence under the assumption of constant percentage atrophy rates prior to the start of the study.

Results: We found no significant difference in whole brain, temporal lobe or ventricular volume between patients and controls at baseline. Medial temporal lobe volumes were smaller in cases than controls, with the differences attaining statistical significance for the right hippocampus ($P = 0.02$) and EC ($P = 0.04$). We demonstrated significantly increased rates of whole brain, temporal lobe, hippocampus and EC atrophy in patients compared to controls ($P < 0.05$). Using averaged medial temporal lobe measurements, and extrapolating to a point of divergence, we calculated that medial temporal lobe atrophy commenced 3.5 years (95% CI 0.7–7.5) prior to the commencement of the study.

Conclusions: Our results suggest that medial temporal lobe atrophy is occurring years prior to the onset of symptoms. If, as is likely, atrophy rates accelerate as the disease progresses, medial temporal atrophy may commence even earlier than these results suggest.

(32) STRUCTURAL CEREBRAL CHANGES IN MILD COGNITIVE IMPAIRMENT

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In the present study we investigated the morphological changes in subjects with mild cognitive impairment (MCI) revealed by quantitative magnetic resonance imaging (MRI). Twenty-one subjects with cognitive impairment according to modified criteria of aging-associated cognitive decline (AACD) and 22 healthy controls were recruited from the interdiscidiplinary longitudinal study on adult development and aging (ILSE) and were compared with 12 patients suffering from mild Alzheimer's disease (AD) (NINCDS–ADRDA guidelines). The volumes of the following brain structures were assessed: total intracranial compartment, cerebrospinal fluid compartment, whole brain, and medial temporal substructures (hippocampus and parahippocampal gyrus). Subjects with mild cognitive impairment showed a significantly reduced volume of the right parahippocampal gyrus compared with healthy controls. Volumes of the other regions and structures did not differ between the MCI group and controls. In AD patients all morphometric parameter except whole brain and CSF volume differed significantly compared to the other groups. The volumetric and neuropsychological findings of the present study support the hypothesis that mild cognitive impairment—at least in some of the affected individuals—can be seen as a preclinical stage of AD and that atrophy of the parahippocampal gyrus might be useful as an early marker of AD.

(33) BRAIN VOLUMETRY TO CHARACTERIZE MILD COGNITIVE IMPAIRMENT. A POPULATION-BASED STUDY IN ELDERLY SUBJECTS AGED 75–85

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Objective: The study aims at characterizing mild cognitive impairment (MCI) based on MR volumetry.

Methods: 3D T_1-weighted MR images were obtained in a randomly selected population-based sample with normal cognition (NC) ($n = 35$, 14 males) and MCI ($n = 37$, 72 and 12 males), respectively, and an age-matched referent group with dementia ($n = 33$, 12 males) (mean age $\pm$ S.D.: 78.7 ± 2.81, mean MMSE $\pm$ S.D.: 25.46 ± 4.25). The brain compartments intracranial volume (ICV), brain volume (BV), white matter volume (WMV), gray matter volume (GMV), internal CSF volume (iCSF), external CSF volume (eCSF) were segmented automatically. Hippocampal volume estimates (HcV) were derived by manual outlining.

Results: Only in females with MCI, significant group differences in HcV, normalized HcV and ICV were found as compared to NC. All volumetric measures differed between normal cognition and dementia in both gender. Repeated measures ANOVA suggested that the hippocampus differed in shape, not only in size, over the cognitive states. Discriminant function analysis based on all volumetric measures revealed a significant function only in women leading to a 84% correct classification of NC and MCI. Absolute hippocampal volumes discriminated the groups better than the normalized volumes. Hippocampal asymmetry (Right > Left) was preserved in women with MCI, but not in men with MCI.

Conclusion: MCI can be characterized by smaller hippocampal volumes and a lower cerebral reserve as compared

to normal in elderly women, whereas the amount of global brain atrophy discriminates MCI from dementia. Although the lack of significance of these findings in men could be due to small group size, a number of findings in this study point towards possible gender differences which require further exploration.

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(34) ASSOCIATION OF MMSE AND CORTICAL GLUCOSE METABOLISM DURING RESTING AND ACTIVATION STATES IN ALZHEIMER'S DISEASE BEFORE AND AFTER PARTIAL VOLUME CORRECTION

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Background: Partial volume effects (PVE) in 18FDG Positron Emission Tomography (PET) lead to an artificial decrease in measured activity of regional glucose metabolism. This effect is accentuated in populations with brain atrophy such as Alzheimer's disease (AD).

Objective: We studied the association between regional brain glucose metabolism and Mini-Mental State Exam (MMSE). In addition, we investigated the effects of PVE correction on the association between MMSE and brain glucose metabolism.

Method: Regional cerebral glucose metabolism was measured in the resting state and during passive audiovisual stimulation (watching a movie) in a group of 15 AD patients (average MMSE $= 23.7 \pm 3.5$, range: 17–29) using PET with two sequential FDG injections. Each patient's PET data was corrected using the data from a high-resolution MRI scan of the patient. The association between MMSE and glucose metabolism were inferred from the correlation coefficient between the MMSE scores and the PET measurements.

Results: The correlation coefficient values between dementia severity and resting glucose metabolism are significant in left hemisphere: fusiform gyrus, inferior and middle occipital gyrus, inferior, middle and superior temporal gyrus, posterior cingulate, inferior parietal gyrus, angular gyrus, and inferior and middle frontal gyrus. In the right hemisphere the areas are: lingual gyrus, inferior, middle and superior temporal gyrus, inferior parietal gyrus, inferior and middle frontal gyrus. During audiovisual stimulation, the additional areas of significant correlation were in the left cuneus, and right inferior occipital gyrus. After atrophy correction, the regions of significant correlation do not change.

Conclusions: The audiovisual activation paradigm is more sensitive to increasing neuronal dysfunction with increasing dementia severity compared to the resting paradigm. The significant correlations between MMSE and glucose metabolism are not an artifact of brain atrophy.

(35) MEASUREMENT OF LOBE VOLUMES ON MAGNETIC RESONANCE IMAGING SCANS: APPLICATION TO ALZHEIMER'S DISEASE VOLUMETRIC CHANGES

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Background: It is a challenge to reliably measure the lobar volumes from magnetic resonance imaging data.

Objective: To develop a landmark-based method for volumetric segmentation of the brain into the four cerebral lobes from MRI images.

Method: The segmentation method relies on a combination of anatomical landmarks and geometrical definitions. The first step is a segmentation of the four lobes on the surface of the brain. The internal borders between the lobes are defined on the axial slices of the brain. The intra- and inter-rater reliability was determined from a group of 10 healthy control subjects. The method was applied to a group of 30 Alzheimer's disease patients and a group of 24 healthy controls.

Results: The intra-rater relative error (and intra-class correlation coefficient) of the lobar volume measures ranged from 0.81 to 3.85% (from 0.97 to 0.99). The inter-rater relative error (and intra-class correlation coefficient) ranged from 0.55 to 3.09% (from 0.94 to 0.99). All four lobar regions were significantly smaller in Alzheimer's disease patients compared to age-matched healthy controls ($P < 0.05$). The gray matter volumes were significantly smaller in the Alzheimer's disease patients with the exception of the right frontal lobe where there was a trend to significance.

Conclusion: This landmark-based method can accommodate morphological changes in brain structure related to disease and normal developmental changes. We show that there is a significant decrease in total and gray matter volume in Alzheimer's disease patients that is concurrent to the focal atrophy that has been previously found. The technique described is reliable and can be applied to studying the structural correlates of cognitive change and neurodegeneration due to disease.

(36) FUNCTIONAL CONSEQUENCES OF SUBCORTICAL WHITE MATTER CHANGES IN ALZHEIMER'S DISEASE

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Introduction: Although confluent areas of white matter disease (WMD) are seen in 30% of Alzheimer's patients, the functional significance of WMD in AD remains unclear. WMD is related to frontal/executive functions in vascular dementia, but there is limited data on the relationship between WMD and frontal/executive functions in AD.

Objective: The objective of this study was to examine the impact of WMD on frontal/executive functions and activities of daily living (ADLs) in AD.

Method: Participants included 40 AD patients (mean age = 77.82 years, mean MMSE = 21.0) and their caregivers. Tests of executive cognitive functioning included the Initiation/Perseveration subscale of the Dementia Rating scale, the Trail Making Test Part B, and the Controlled Oral Word Association Test. Frontal behavioral and ADL assessments included the informant-rated Frontal Systems Behavioral Inventory (FrSBe) and the Lawton & Brody ADL scale, respectively. AD patients were classified as having "minimal–mild" or "moderate–severe" WMD ($n = 20$ per group) on the basis of visual ratings of white matter hyperintensities on axial FLAIR MRI sequences. Ratings were made by a trained MRI rater blind to the cognitive test results.

Results: Multivariate ANOVAs (adjusted for MMSE) revealed significant main effects of group on executive cognitive ($F = 9.99$, $P < 0.01$) and frontal behavioral functions ($F = 4.3$, $P < 0.05$). Post-hoc comparisons revealed that AD patients with moderate–severe WMD performed significantly worse than did those with minimal–mild WMD on all executive tests and on two of three subscales of the FrSBe. AD patients in the moderate–severe WMD group also showed significantly greater ADL impairment than did those in the mild group ($t = 3.9$, $P < 0.05$). Executive cognitive tests accurately classified 90% of AD patients as "high" or "low" ADL scorers (canonical correlation = 0.78, $P < 0.05$).

Conclusion: These findings suggest that WMD contributes significantly to the frontal/executive and related ADL deficits seen in AD patients.

(37) AN ^{15}O PET STUDY OF WORD MEANING IN AD

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Researchers have suggested that in neurodegenerative diseases patients might be recruiting alternative systems to perform the same cognitive tasks as nondiseased individuals. We carried out a ^{15}O PET study which compared the brain correlates of activation for word meanings in elderly normal subjects (ENs) with that of patients with Alzheimer's type dementia (ADs). Subjects made forced-choice semantic judgments about the similarity in meaning between pairs of words; during two scans were of Concrete concepts (e.g. cave-tunnel versus cave-clothes), and two of Abstract concepts (e.g. labor-toil versus labor-wisdom). Besides being slower and less accurate than the ENs, ADs displayed a category effect not seen in the ENs in that they were slower and less accurate on the abstract concepts ($M = 3250$ ms, 93.5%) than on the concrete concepts ($M = 3014$ ms, 96.4%). Analyses of the rCBF indicated that both groups activated the ventral occipital–temporal cortex more for concrete than for abstract concepts, suggesting that activation of the Concrete concepts involves some type of figural processing. rCBF was left lateralized in the ENs but it was bilateral and more distributed in the ADs. More striking, however, was the increase in CBF in the right hippocampus in the ADs but not in the ENs. A review of PET imaging studies indicates that increases in right hippocampus CBF in normal individuals is brought out, in general, during episodic memory tasks which require the encoding and/or recognition of figurative material. This finding is similar to a previous PET study (Chertkow et al., 1999) in which ADs but not ENs activated the *left* hippocampus during difficult picture naming. We propose that in both of these semantic tasks (picture naming, judgement of meaning) ADs activate episodic memory circuits to supplement their degraded semantic memory system.

(38) ^{99M}TC-HMPAO SPECT IMAGE ANALYSIS IN DEMENTIA WITH LEWY BODIES AND ALZHEIMER'S DISEASE USING STATISTICAL PARAMETRIC MAPPING

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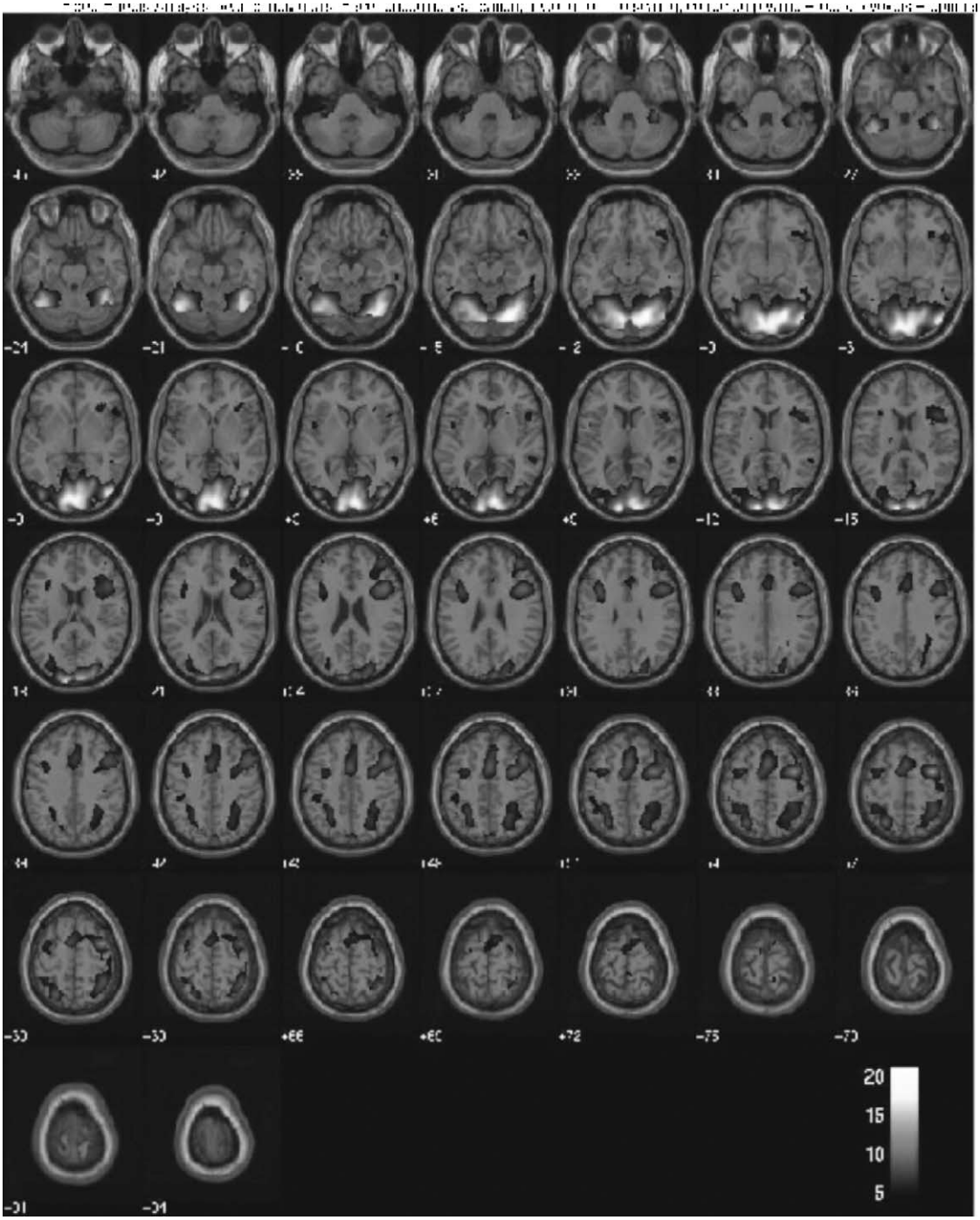
Methods: The purpose of this study was to investigate differences in rCBF using ^{99m}Tc-HMPAO SPECT images in subjects with DLB compared to AD and age-matched controls using the Statistical Parametric Mapping (SPM99) technique. SPM, was carried out on ^{99m}Tc-HMPAO SPECT scans obtained from patients diagnosed with Consensus criteria DLB ($n = 23$, mean age = 75.9 years), NINCDS/ADRDA AD ($n = 48$, mean = 77.9 years) and healthy age-matched controls ($n = 20$, mean = 75.4 years).

Results: Applying a height threshold of ($P \leq 0.001$ uncorrected), the SPM$\{t\}$ map showed large perfusion deficits in the parietal, temporoparietal and frontal regions of the brain

in the AD group compared with the control subjects. In addition, significant reductions in perfusion in the parietal, occipital and frontal regions were found in the DLB group with respect to normal control subjects. Comparing dementia groups (height threshold $P \leq 0.01$ uncorrected), yielded perfusion deficits in both the parietal (Brodmann area 7) and occipital regions of the brain in DLB compared with AD, a region which included part of the primary visual cortex and visual association areas.

Conclusion: Compared with AD, DLB is associated with hypoperfusion in posterior parietal and occipital regions, which may be important in understanding the prominent visuospatial dysfunction, and visual hallucinosis, which is characteristic of the disorder.



(39) BRAIN ACTIVATION MEASURED WITH FMRI IN MILD COGNITIVE IMPAIRMENT

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Background: Mild cognitive impairment (MCI) is a heterogeneous disease-entity comprising many different cognitive disorders, including early Alzheimer's disease (AD). Common neural pathways may underlie changes in different MCI-patients. Functional MRI (fMRI) may detect both differences and commonalities relevant for early diagnosis of underlying disease.

Objective: To study brain activation with fMRI, using a working memory (WM) and a face encoding (FE) paradigm in elderly controls, MCI and mild AD. Here we report the feasibility of fMRI in an ongoing MCI-study.

Methods: So far, five MCI-patients were studied (one male, four females, age: 70±8.8 years, MMSE: 25.8±0.8, CDR0.5 by definition) while performing a parametric n-letter back WM task with three conditions: attention, easy WM, and increased WM load, and an FE task contrasting FE to fixation.

Results: Test scores corrected for false-positive and -negative hits were all significantly above chance levels (0.89 ± 0.17, 0.93 ± 0.16, 0.65 ± 0.21 for attention, easy and increased WM load, respectively, and 0.34 ± 0.06 for FE). The n-back task produced strong activation in frontal and parietal structures bilaterally and the anterior cingulate gyrus. FE activated the occipital lobes and ventral and dorsal pathways in both hemispheres. Main effects further included the middle frontal gyrus bilaterally, anterior cingulate, right inferior frontal and left superior frontal gyrus. No activation was seen in MTL structures.

Conclusions: fMRI in MCI is feasible. Activation during Working Memory performance was similar to that observed previously in young healthy controls. Contrary to earlier results in healthy subjects, no activation was seen in the MTL during face-encoding. Whether this is due to a lack of power or to a common disease-pathway in MCI will be determined by inclusion of more patients and controls.

(40) AUTOMATED ASSESSMENT OF WHITE-MATTER INTERGRITY USING DIFFUSION TENSOR IMAGING: EFFECTS OF AGING AND DEMENTIA STATUS

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Background: Alterations in cerebral white matter have been noted in both advancing age and dementia of the Alzheimer type (DAT). However, the degree of change in the microstructure of white matter across the lifespan and the extent of differences between older adults and individuals with DAT are not fully established.

Objective: The primary goal of this study was to quantitatively assess age- and dementia-related changes in white matter microstructure using diffusion tensor (DT) imaging.

Method: DT images were acquired in 25 young adults (mean age $= 22 \pm 4.4$ years), 25 individuals with very mild to mild DAT (mean age $= 76 \pm 1.10$ years) and 25 non-demented older adults (mean age $= 77 \pm 1.39$ years). Participants were selected from an online archive of structural data at Washington University and older adults were identified as demented or non-demented based on the Clinical Dementia Rating scale. DT images for each participant were spatially transformed into a standard atlas space using target atlases consisting of data from younger and older adults, and motion corrected for between-acquisition movement. After transformation into atlas space, average images for each group were obtained to assess the overall pattern of differences. Measures of diffusion anisotropy were calculated for each individual in frontal, temporal, parietal and occipital white matter.

Results: We observed age-associated loss of white matter anisotropy with evidence that the loss was more pronounced in anterior than posterior regions. Contrary to expectations that dementia per se would manifest as changes in diffusion properties of white matter beyond age, the disparity between individuals with DAT and non-demented older adults appeared less robust.

Conclusions: Healthy aging and DAT are characterized by significant deterioration in white matter integrity as indexed by DT imaging. Our results highlight the efficacy of DT imaging for assessment of white matter microstructure in these populations and the value of transformation to standard atlas space for observation of group differences. (This abstract will also be presented at the 8th International Conference on Alzheimer's Disease and Related Disorders.)

(41) PRELIMINARY COMPARISON OF FMRI PARADIGMS FOR DETECTING DEMENTIA

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Under the auspices of a VA Research Enhancement Award Program (REAP) and the State of California Alzheimer's Disease Program we are comparing the discriminative validity of a set of fMRI paradigms for detecting the presence of Alzheimer's disease. Preliminary data from the follow-

ing paradigms will be presented: effects of stimulus repetition in semantic classification of words, effects of stimulus repetition in recognition memory for words, effects of stimulus repetition in semantic classification of pictures, effects of stimulus repetition in recognition of pictures, effects of stimulus repetition on face processing. Differences between demented and nondemented subjects in task performance and BOLD response will be presented, and task comparisons discussed. Within these studies we are also comparing fMRI results in Spanish/English bilingual patients and controls to monolingual English-speaking subjects. Preliminary results of the effects of bilinguality on task performance and BOLD effects will also be presented.

(42) CORTICAL THICKNESS IN ALZHEIMER'S DISEASE

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Introduction: Previous studies—mostly relying on manual measurements—have repeatedly demonstrated specific atrophy in Alzheimer's disease (AD) compared to normal controls [1]. The object of this study was to examine the usefulness of a fully automated cortical thickness measure to investigate changes occurring in AD.

Methods: Forty-one T_1 scans (25 AD and 17 controls) from the Klinikum der Innenstadt, Ludwig-Maximilian University, Munich, Germany, were registered to Talairach space [2] and corrected for non-uniformity artifacts [3]. The MR images were classified into white matter, gray matter, and CSF [4], followed by an extraction of inner and outer surfaces using deformable models [5], which provides the advantage of colocalizing vertices across brains, allowing for population statistics. Cortical thickness was measured at each vertex using Laplace's equation [6,7] (reimplemented locally). Statistical analysis was performed at each vertex, employing clinical diagnosis, or Mini-Mental State Exam (MMSE) scores.

Results: In the main group analysis, significant differences in cortical thickness occurred in the medial temporal lobes, the orbito-frontal cortex, the posterior cortex, and the posterior cingulate. In the temporal lobes, effects were strongest in the left entorhinal cortex and left parahippocampal gyrus (F values = 20–40). The frontal lobes demonstrated an effect bilaterally in the orbito-frontal areas (F = 20–37). In the posterior cortex significant effects existed bilaterally in the superior and inferior (F = 8–15) parietal lobules. AD subjects also showed decreased cortical thickness in the associative visual areas bilaterally (F = 17–20) and the posterior cingulates (F = 27–40). Regression against MMSE scores showed additional significant results in both the ventral and dorsal visual pathways along with a left-hemisphere dominant effect in the major language areas. Noticeable here were Broca's (F = 33 left, 12 right) and Wernicke's area (F = 28 left, 4 right).

Discussion: The results confirm previous findings of specific atrophy in AD, especially in the limbic system and its cortical connections. It was intriguing to find a precise anatomical outline of the entorhinal cortex as a result of the statistical analysis, since it is discussed as being affected early and profoundly in the course of AD. Moreover, the effects in the language areas seen only in the MMSE regression point to the importance of language function in determining MMSE scores.

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(43) FUNCTIONAL MRI OF MEMORY: EFFECTS OF AGING AND DEMENTIA STATUS

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Background and objective: Changes in memory-related information processing occur at both behavioral and neural levels as a result of normal aging and dementia of the Alzheimer type (DAT). We studied these changes using functional MRI (fMRI) of young adults, nondemented older adults, and older adults with mild to very mild DAT as assessed using the Clinical Dementia Rating (CDR) scale. We specifically address the question of whether participants with early DAT (CDR = 0.5 or 1) are characterized by changes in frontal cortex that are advanced for their age. We also asked whether reductions in frontal activation associated with implicit memory (priming) are spared in age and DAT, as is often the case on behavioral measures.

Methods: Functional imaging included blocked and event-related designs using tasks designed to differentially emphasize encoding, priming, and recognition. All older adults also completed a separate session of detailed structural imaging to allow examination of the relations between brain anatomy and functional response.

Results and conclusions: All groups showed robust activations in frontal cortex, demonstrating the feasibility of imaging even very old (up to 90+ years) and mildly demented participants. Preliminary analysis of 20 participants suggested that activation of these frontal regions along inferior frontal gyrus during verbal encoding, typically left-lateralized in young adults, becomes more bilateral with advanced age. These results specifically suggest that while changes in frontal cortex recruitment occur with aging, these changes may not be accelerated in early-stage dementia.

(44) NOVEL FINDINGS IN TWO CASES OF BIOPSY-PROVEN SMALL ARTERY DISEASE: SPONTANEOUS CEREBRAL HEMORRHAGE IN CADASIL AND SEVERE WHITE MATTER EDEMA IN AMYLOID ANGIOPATHY

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We report two cases with novel findings in biopsy-proven cerebral small artery disease. In the first case a 57-year-old man with a 6-year history of multiple sclerosis was admitted with a 4–5-day history of slurred speech and left sided weakness. MRI revealed a moderate size hematoma in the right frontal lobe and severe subcortical white matter disease involving the corpus callosum and anterior temporal white matter. Biopsy of the right frontal lobe revealed thickened arterioles with degeneration of the smooth muscle layer throughout the brain and meninges. Gene testing was positive for a known notch3 mutation. In the second case a 67-year-old non-hypertensive woman without dementia developed a stuttering neurological course accompanied by lobar and microhemorrhages and severe fluctuating levels of white matter edema on MRI biopsy of the right frontal lobe revealed severe amyloid angiopathy (AA) without evidence of amyloid plaques. Segmental edema improved after treatment with corticosteroids. MRI examples and biopsy slides will be presented.

Discussion: Although cerebral microbleeds have been reported in CADASIL, this is the first case report of spontaneous cerebral hemorrhage in CADASIL Severe fluctuating white matter edema has rarely been reported in AA and has been reported in one case of biopsy-proven CADASIL.

Conclusions: Spontaneous hemorrhage can occur in CADASIL and anticoagulants should be used with caution. We propose that amyloid deposition can produce a fluctuating disturbance in the integrity of the blood brain barrier.

(45) PET ACTIVATION IN MCI AND AD PATIENTS

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Objective: It is of utmost importance for new treatment strategies in MCI and AD to find sensitive clinical instruments and biological markers for early detection. Furthermore, a greater knowledge of the relationship between functional regional brain activity and cognitive performances will cast light on important neuronal networks and brain plasticity during neurodegenerative processes. The data so far obtained suggest that identification of early functional changes in brain can be made by imaging techniques such as positron emission tomography (PET) even at a presymptomatic stage of the disease. A typical feature of AD is impairment of attention. In order to explore the brain regions responsible for sustained attention we have investigated regional blood flow and nicotinic receptors using PET in MCI and AD patients.

Methods: Changes in cerebral blood flow and nicotinic receptors were studied in 11 AD and 4 MCI patients prior and during a rapid visual information processing task (RVIP) (sustained attention). The AD patients received treatment with rivastigmine (dose range: 4–12 mg) for 12 months and the PET activation studies were performed prior and after 3 and 12 months of rivastigmine treatment.

Results: The MCI and AD patients regional specific differences in task-related changes in cerebral blood flow during sustained attention. A deactivation pattern observed in the prefrontal cortex of MCI patients was not seen in AD patients but unless the AD patients had been treated with rivastigmine for 3 months. Changes in nicotinic receptor binding was found during attentional task both in MCI and AD patients. Treatment with rivastigmine for 3 months increased the number of cortical nicotinic receptors in AD patients and a different pattern of receptor activation pattern was seen during attentional task.

Conclusions: Somewhat different activation patterns are observed in brain of MCI and AD patients during sustained attention reflecting compensatory mechanism of distressed networks impaired by the disease processes. Cholinesterase inhibitors may improve the regional networks in AD patients.

(46) DIFFERENTIAL ACTIVATION OF THE PERIRHINAL CORTEX AND HIPPOCAMPUS IN ENCODING AND RETRIEVAL OF NOVEL PICTURE-PAIRS

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Background: It is well-established in non-human primates that the medial temporal lobe (MTL) structures, the hippocampus and the entorhinal and perirhinal cortices, are

necessary for declarative memory encoding. In humans, the neuropathological and neuropsychological changes in early Alzheimer's disease (AD) further suggest a role for the rhinal cortex in the consolidation of new events into memory. However, the precise role of the MTL structures in memory formation in humans is largely unknown.

Objective and methods: To determine the participation of the MTL structures in long-term memory processes, the neural correlates of encoding and retrieval of novel picture-pairs were studied using functional magnetic resonance imaging (fMRI) in 12 young control subjects. fMRI was performed on a 1.5 T scanner using a gradient-echo EPI sequence. Sixteen oblique axial slices were acquired (voxel size: 4.0 mm × 4.0 mm × 5.0 mm).

Results: The most striking finding in the MTL activation pattern was the activation of the perirhinal cortex in the encoding-baseline and encoding-retrieval comparisons ($P < 0.00001$; unpaired *t*-test). In contrast, no perirhinal cortex activation was detected in the retrieval-baseline or retrieval-encoding comparisons. The perirhinal activation was located in its transentorhinal subarea, in the medial bank of the collateral sulcus. In contrast, the hippocampal activation was detected in both encoding and retrieval conditions. A main effect of the cognitive condition on the brain activation ($F(2, 14) = 69.3$, $P < 0.0001$; ANOVA), and a significant interaction between the condition and the anatomical area ($F(2, 14) = 10.3$, $P = 0.0002$) were observed.

Conclusions: These data suggest that encoding, but not retrieval, of novel picture-pairs activates the perirhinal cortex. Detection of encoding-related activity in the rhinal cortex is consistent with clinical findings in AD, and supports the view that these cortical areas have a distinct role in the episodic memory formation.

(47) SEX DIFFERENCES IN REGIONAL CEREBRAL BLOOD FLOW: CLINICAL IMPLICATIONS FOR ALZHEIMER'S DISEASE

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Background: Some epidemiologic data indicate that risk for Alzheimer's disease (AD) in women is 1.5–3 times that in men, even after adjusting for greater longevity in women. The reasons for this difference are unclear.

Objective: To investigate sex differences in regional cerebral blood flow (rCBF) in specific brain regions as a contributor to a greater risk for AD in women.

Method: Positron emission tomography and 15-oxygen labeled water were used to measure rCBF in 83 non-demented men ($n = 46$; age: 70.9 ± 7.3 years) and women ($n = 37$; age: 70.6 ± 7.9 years) at three time points: baseline, Year 3, and Year 5. Sex differences in the pattern of rCBF during a resting condition were investigated using Statistical Parametric Mapping 99.

Results: Across all time points, cross-sectional analyses indicated that men had significantly higher relative rCBF in a number of temporal and frontal regions, including hippocampus, parahippocampal gyrus, inferior and middle frontal regions, and in cerebellar vermis. There were no regions where women had higher relative rCBF.

Conclusion: Sex differences in rCBF in older adults are pronounced in selective brain areas critical to memory. Importantly, preclinical reductions of blood flow and metabolism in hippocampal and entorhinal regions have been shown to be associated with AD and with the apolipoprotein E ε4 risk factor for AD. Furthermore, we have previously shown that hormone replacement therapy (HRT) is associated with longitudinal increases in mesial temporal rCBF in postmenopausal women. Thus, we suggest that reduced mesial temporal rCBF in women compared with men contributes to their greater risk for AD by bringing them closer to a critical threshold of neural activity, below which dementia occurs. HRT, which appears to reduce the risk for AD in postmenopausal women, may thus offer protection against a diagnosis by raising neural activity in temporal and frontal brain regions critical for intact memory functioning.

(48) FMRI OF WORKING MEMORY IN ALZHEIMER'S DISEASE AND FRONTOTEMPORAL DEMENTIA

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Background: Many functional MRI (fMRI) studies have shown brain activation in the prefrontal cortex (PFC) and parietal cortex in healthy subjects during so-called n-back working memory (WM) tasks.

Objective: To study with fMRI the functional system of WM in patients with mild AD and patients with frontotemporal dementia (FTD), to determine brain regions of both common and differential activation. The hypothesis is that the WM network as seen in healthy subjects is relatively spared in AD, but impaired in FTD.

Methods: Seven patients with mild AD (five males, two females, age: 63 ± 11 years) and seven patients with FTD (five males, two females, age: 55 ± 9 years) were scanned using fMRI while performing a parametric n-back working memory task with four conditions: rest, attention, easy WM, and increased WM load. Group analysis included detailed inspection of individual signal change.

Results: Test scores on a scale of 0 (chance level) to 1 (max) for attention, easy WM and increased WM load in AD were

0.99±0.01, 0.85±0.25, 0.74±0.24; and in FTD 0.94±0.12, 0.93±0.14 and 0.76±0.27. Although FTD patients showed activation in the PFC and parietal cortex, direct statistical comparison showed in these regions significantly less activation in FTD compared to AD, and also in temporal and cingulate cortex. The reversed effect (i.e. more activation in FTD) was seen in the cerebellum.

Conclusions: Applying a parametric WM task we found an activation pattern resembling healthy subjects for this WM task (i.e. PFC and parietal cortex). Interestingly, these areas showed a decreased response in FTD compared to AD, while there was no difference in WM performance. This result is in agreement with our hypothesis of more impairment of the WM network in FTD than in AD. On the other hand, FTD patients showed increased cerebellar activation, which might be explained as a compensation mechanism for the decreased functioning of the frontal–parietal network.

(49) CORTICAL REPRESENTATION OF THE MODIFIED TRAIL MAKING A TEST—ACCESS TO BILATERAL PARIETAL AND OCCIPITAL CORTICAL FUNCTION IN AD

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Background: Alzheimer's disease (AD) affects a wide range of cognitive functions, including memory and language, but also visuo-constructive performance and attention. Neuropsychological batteries for dementia are often biased towards language and memory impairment.

Objective: To assess the cortical representation of a modified version of the trail making A test, which is included in the Nuremberg Age Inventory ("Zahlenverbindungstest"—ZVT).

Methods: We studied 45 patients with the clinical diagnosis of probable AD. In a first group of 30 patients only resting state F-18 FDG PET-scans were performed (rest group). In a second group of 15 patients two F-18 FDG PET-scans (185 MBq) were performed in a single session (activation group): (1) resting condition (2) presentation of the sequence of a movie (passive audiovisual stimulation). Order of the scans was randomized, correction for persisting activity of the first scan was performed. Atrophy correction was done in the activation group PET scans based on individual MRI. PET-data were normalized stereotactically (Neurostat, University of Michigan, USA). Voxelwise correlations were performed between PET-scans and ZVT.

Results: ZVT was correlated with metabolism in bilateral superior parietal lobes in the rest group. In the activation group, correlations were additionally found in bilateral occipital lobe, including Brodman areas 17 and 18, both during rest and stress conditions. Results remained essentially unchanged after atrophy correction.

Conclusion: These results indicate that the ZVT may functionally represent the bilateral superior parietal and occipital lobes in AD, cortical areas which are only poorly represented in neuropsychological test batteries.

(50) IN VIVO MAPPING OF NEOCORTICAL NEURONAL DEGENERATION IN ALZHEIMER'S DISEASE—STUDIES OF THE CORPUS CALLOSUM WITH MRI, EEG AND PET

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Background: Pathological studies in Alzheimer's disease (AD) indicate specific loss of layer III and V large pyramidal neurons in association cortex. These neurons give rise to long intracortical connections, projecting through the corpus callosum, in an anterior–posterior topology.

Objective: We hypothesized that regional corpus callosum atrophy may be an in vivo marker for neocortical neuronal loss in AD.

Methods: In a subsequent series of studies in AD patients and healthy controls using MRI, ^{18}FDG-PET and EEG, we investigated the effect of white matter hyperintensities (WMH) on total and regional corpus callosum size and correlations between pattern of corpus callosum atrophy and cortical metabolic decline as well as intracortical coherency.

Results: Corpus callosum area was significantly reduced in AD patients compared to controls, with the greatest changes in the rostrum and the splenium. The regional pattern of corpus callosum atrophy was independent of WMH load and correlated significantly with pattern of regional metabolic decline measured with ^{18}FDG-PET, the degree of cognitive impairment and regional decline of bilateral intracortical-coherency in EEG in AD patients. In a longitudinal study, rates of corpus callosum atrophy were significantly greater in AD patients than in controls and correlated with progression of clinical dementia severity in AD.

Conclusion: These results indicate that corpus callosum atrophy in AD represents loss of callosal efferent neurons in corresponding cortical regions. As these neurons are a

subset of cortico-cortical projecting neurons, corpus callosum atrophy may serve as a marker of progressive neocortical neuron loss in AD.

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(51) FMRI OF WORKING MEMORY FOR OBJECTS IN MCI AND ALZHEIMER'S DISEASE

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Background: Functional MRI (fMRI) has been utilized to identify the neural correlates of age-related and neurodegenerative disease associated changes in cognitive functions. Working memory (WM), an essential component of cognitive functioning, has been shown to decline with aging.

Objective: The aim of this study was to evaluate fMRI of brain regions serving WM in patients with Azheimer's disease (AD), mild cognitive impairment (MCI), and controls.

Methods: Eleven AD patients (55–83 years), seven MCI patients (62–77 years) and nine controls (54–71 years) underwent fMRI using a 1.5 T scanner. Functional images of the brain were acquired while the subjects were performing an *n-back* WM task for objects. Regions of activation in the entire brain were identified in each subject. The task performance was compared between the groups using MANOVA.

Results: Task performance was not significantly different between the groups. Functional images of the brain were obtained in all subjects. Activation was observed in the following regions: bilateral fusiform gyrus, hippocampus, parahippocampal gyrus, visual cortex, bilateral frontal (BA6/8, BA9/46, BA44/45), anterior cingulate (BA24/32), and parietal cortex (BA7/40). The clusters of activation observed in AD and MCI patients showed a greater extension compared to those of controls. Examples of scans from individual subjects are shown in Fig. 2a–c. Additional regions of activation were also detected in AD and MCI patients.

Conclusions: The WM task for objects evoked activation in a widely distributed neural network consistent with the previous fMRI studies. Compared to controls, AD and MCI patients showed an increased extent of activation in the network and recruitment of additional regions. The observed difference might suggest that AD and MCI patients suffering from cognitive decline are recruiting additional regions to meet the processing demands for working memory maintenance. These results are consistent with the hypothesis that MCI lies along the continuum of AD.

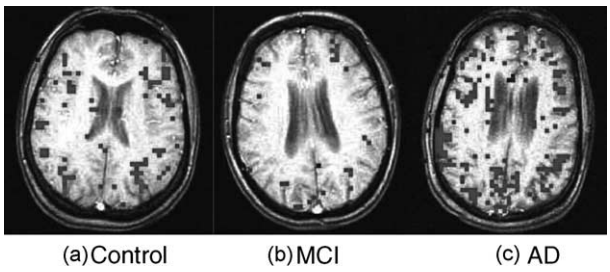

Fig. 1.

(52) LONG TERM EFFECTS OF ERT ON THE HIPPOCAMPUS AND MEMORY

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Background: There has been a great deal of interest regarding the neuroprotective effect of estrogen replacement therapy (ERT) against memory decline in aging. To date, epidemiological and neuroimaging studies have been inconclusive as to whether estrogen protects against memory decline, partly because the duration of estrogen use often ranges from only a few to many years. However, it stands to reason that exogenous estrogen must be continuous to protect against cumulative cell loss.

Objective: To compare memory functioning in long term, continuous ERT users to never users using fMRI.

Methods: Ten healthy, cognitively normal elderly women (six ERT+, four ERT−) underwent a brief neuropsychological evaluation followed by scanning. The fMRI task was designed to assess the potentially rapid adaptation to new repeating stimuli. Participants viewed four faces, repeating seven times for each of the three runs (different sets of faces). They were instructed to learn each face.

Scanning parameters: TE = 40 ms, TR = 3000 ms, FOV = 240 mm, matrix = 64 × 64, number of slices = 32, slice thickness = 4.2, in-plane resolution: 3.75 mm × 3.75 mm.

Statistical analysis: An event-related analysis in SPM99 was conducted. Adaptation was modeled using Activation × Presentation interaction reflecting a negative (adaptation) slope followed by a Random Effects analysis comparing the ERT groups. An anatomical mask of the hippocampal formation was used to constrain the analysis to the mesial temporal region.

Results: Adaptation slopes were found in the right anterior hippocampus showing greater hippocampal activity for the group of women with long-term ERT use compared to never users.

Conclusions: These results suggest that better hippocampal activity is observed in older women who are receiving long-term ERT compared to never users. Further studies are planned to address both short-term and long-term effects of ERT on hippocampal functioning.

(53) AUTOMATED ASSESSMENT OF ATROPHY PROGRESSION IN A CASE OF PROGRESSIVE APHASIA

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Background: Individuals with eventual diagnoses of dementia vary in terms of relative degrees of specific cognitive impairments at onset. Occasionally, early presentation can involve focal progressive aphasia and a left-lateralized atrophy pattern. A continued preferential language decline and selective atrophy of the left hemisphere are often assumed in such cases.

Objective: To quantify hemispheric atrophy rates in progressive aphasia over time.

Method: We followed a male participant (age: 66 years), who presented with progressive non-fluent aphasia, acquiring multiple high-resolution anatomic MRI images over 3 years (four time points). At onset, the participant presented with prominent language difficulties, markedly larger ventricles on the left side and reduced left posterior cortical tissue. Neuroradiological assessment did not indicate the existence of a stroke or other recent pathology. Critically, we quantified the loss of tissue over time using automated atrophy assessment.

Results: The absolute and relative rates of left and right hemisphere atrophy progression were nearly identical. The initial left and right CSF levels progressed from 30 to 36% and 25 to 30.0% over the 3 years, respectively. Realignment and direct comparison of anatomic data confirmed the similar and progressive nature of tissue loss in both hemispheres. Concurrent neuropsychological testing revealed the onset of short-term memory and visuospatial impairment in the context of a DAT-like profile (Clinical Dementia Rating (CDR) = 1).

Conclusions: These data suggest that marked language difficulties arose because of reduced capacity in left-hemisphere regions that likely existed before dementia began. We speculate that, in the context of an aggressive bilateral degenerative process, symptoms associated with his limited left hemisphere reserve were prominent early revealing his atypical profile associated with progressive aphasia. Quantification of atrophy over time can increase understanding about the relation between initial brain states and patterns of progression in the dementias.

(54) AUTOMATED METHOD USING ITERATIVE PRINCIPAL COMPONENT ANALYSIS FOR DETECTING BRAIN ATROPHY RATES FROM SEQUENTIAL MRI IN PERSONS WITH ALZHEIMER'S DISEASE

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Background: Using a semi-automated digital subtraction (DS) algorithm to compare sequential magnetic resonance images (MRIs), Fox et al. have shown abnormally high rates of whole brain atrophy in patients with Alzheimer's dementia, and mild cognitive impairment (MCI). We recently developed a fully automated method using iterative principal component analysis (IPCA) to compute whole brain atrophy rates.

Objective: To compare the IPCA method with the established DS method in characterizing abnormal whole brain atrophy rates in patients with Alzheimer's dementia (AD).

Methods: The IPCA method treats baseline and follow-up MRI voxel intensities as paired variables and brain locations with significant intensity differences are identified using their distance from the PCA's major axis. Baseline and follow-up MRIs from eight AD patients (54–58 years of age) and eight normal controls (also 54–58 years of age) were coregistered using SPM99 and analyzed blindly using both the IPCA and DS methods.

Results: The AD patients had significantly higher atrophy rates (percent brain volume decline per year) than the normal controls using both the IPCA method (0.93–0.22 versus 0.20–0.12, $P = 5e{-}7$) and the DS method (2.24–0.87 versus 0.08–0.26 $P = 5e{-}6$). Atrophy rates detected by the IPCA and DS methods were closely correlated ($r = 0.91$, $P = 3e{-}6$). In the AD patients, lower baseline MMSE scores were associated with higher atrophy rates using both methods (IPCA: $P = 0.04$; DS: $P = 0.002$).

Conclusion: The PCA method can be used to automatically characterize whole brain atrophy rates from sequential MRIs in AD patients.

(55) WHOLE BRAIN ATROPHY RATES IN COGNITIVELY NORMAL PERSONS AT GENETIC RISK FOR ALZHEIMER'S DISEASE

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Background: Using a semi-automated digital subtraction (DS) algorithm to compare sequential magnetic resonance images (MRIs), Fox et al. found abnormally high rates of whole brain atrophy in patients with Alzheimer's dementia (AD) and mild cognitive impairment (MCI) and in persons at risk for an autosomal dominant form of AD who subsequently developed symptoms. We recently developed a fully automated iterative principal component analysis (IPCA) method and found that it was comparable to the DS method in its ability to differentiate whole brain atrophy rates in AD patients from those in normal elderly controls. In another study, we characterized abnormal 2-year declines in positron emission tomographic measurements of the cerebral metabolic rate for glucose in cognitively normal carriers of the apolipoprotein E (APOE) ε4 allele, a common Alzheimer's susceptibility gene.

Objective: To measure rates of whole brain atrophy in cognitively normal persons with two copies, one copy and no copies of the ε4 allele using the DS and PCA methods.

Methods: T_1-weighted MRIs were performed before and after a 2.2-year interval in 10 ε4 homozygotes, 10 ε4 heterozygotes, and 16 ε4 non-carriers 57 ± 4 years of age at the time of their baseline scans.

Results: The three groups did not differ significantly in their gender distribution, age, educational level, duration between MRIs, baseline MMSE or longitudinal MMSE changes. Each MRI analysis method demonstrated a significant group difference in whole brain atrophy rates (ANOVA, DS: $P = 0.043$, PCA: $P = 0.031$). As predicted, APOE ε4 gene dose was associated with increased whole brain atrophy rates (DS: non-parametric Kendall correlation coefficient $\tau = 0.334$, $P = 0.012$; PCA: $\tau \geq 0.312$, $P = 0.017$).

Conclusion: Both the DS and the IPCA methods can be used to characterize abnormally high rates of whole brain atrophy from sequential MRIs in cognitively normal persons at genetic risk for AD.

(56) RELATIONSHIP OF SUBCORTICAL HYPERINTENSITIES TO TREATMENT RESPONSE IN YOUNG AND OLD ELDERLY WITH OUTPATIENT GERIATRIC DEPRESSION: RESULTS OF TWO PLACEBO-CONTROLLED TRIALS

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Background: MRI subcortical hyperintensities (SH) have been implicated in the pathogenesis and clinical course of late-life depression. Most of the information on the effect of SH on treatment response in geriatric depression has been obtained from severely depressed inpatients and there is no controlled clinical trial data on SH and geriatric depression.

Objective: To compare the severity of SH in young and old elderly with depression and examine the relationship between antidepressant treatment response in high versus low levels of SH in two randomized, placebo-controlled trials.

Methods: Participants were geriatric outpatients with mild–moderate depression who participated in 8-week placebo-controlled trials of sertraline (age $\geq$ 60 years, mean age: 69 years, $n = 59$) or citalopram (age $\geq$ 75 years, mean age: 79 years, $n = 114$). Subjects underwent a standardized MRI protocol and were divided into high vs. low SH groups based on visual ratings on axial FLAIR images using a scale.

Results: Age was significantly associated with SH in the sertraline study: The older citalopram group had a greater occurrence of high SH ($\chi^2 = 14.39$, $P < 0.001$) especially in the deep white matter ($\chi^2 = 12.68$, $P < 0.001$) and subcortical gray matter ($\chi^2 = 14.01$, $P < 0.001$). There was no association between hypertension (HTN) and other cardiovascular risk factors and SH severity in the sertraline study. Contrary to our hypothesis, sertraline treatment response did not differ between the high and low SH groups ($P > 0.05$). The depression outcome results for the citalopram group will be presented.

Conclusions: Age is a major determinant of SH in geriatric depression but severity of SH was not associated with response to sertraline in this sample. The relationship between SH and HTN in late-life depression requires further study.

(57) HIPPOCAMPAL VOLUME AND SHAPE VARIATION PREDICTS COGNITIVE DECLINE IN NONDEMENTED ELDER SUBJECTS

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Background: Neuroimaging studies have identified hippocampal volume losses and shape deformations in subjects with very mild dementia of the Alzheimer type (DAT).

Objective: We tested the hypothesis that changes in hippocampal structure predict cognitive decline among nondemented elders.

Methods: High-resolution, T_1-weighted MR scans were collected in 20 male and 29 female nondemented elders (mean age (S.D.): 75 (9) years). The subjects were then annually assessed for dementia using total sum-of-boxes scores from the Clinical Dementia Rating (CDR) scale and general cognition factor scores derived from a neuropsychological battery. At baseline, all subjects were scored as CDR0 (no dementia); the mean (S.D.) length of follow-up was 2.1 (0.6) years. Hippocampal volume and shape variation was assessed using probabilistic transformations of a neuroanatomical template.

Results: Correlations were found between the rate of increase (slope) in sum-of boxes scores and smaller left ($r = -0.49$, $P = 0.001$) and right ($r = -0.41$, $P = 0.003$) hippocampal volumes, total cerebral volumes ($r = -0.44$, $P = 0.001$), and two dimensions of hippocampal shape deformation (eigenvector 1: $r = 0.29$, $P = 0.04$; eigenvector 4: $r = -0.34$, $P = 0.02$). Correlations were also found between the rate of decrease (slope) in general cognition factor scores and smaller left ($r = 0.39$, $P = 0.005$) and right ($r = 0.40$, $P = 0.005$) hippocampal volumes, total cerebral volumes ($r = 0.36$, $P = 0.01$), and one dimension of hippocampal shape variation (eigenvector 4: $r = 0.31$, $P = 0.04$). However, only 4 of the 49 subjects progressed from having CDR scores of 0 (no dementia) to CDR scores of 0.5 (very mild dementia).

Conclusions: These results suggest that smaller hippocampal volumes and hippocampal shape deformations predict cognitive decline in nondemented elder subjects. Further follow-up of these subjects is needed to confirm that the observed increases in sum-of-boxes scores and decreases in neuropsychological testing performance eventually culminate in the diagnosis of DAT.

(58) RATES OF STRUCTURAL CHANGES IN ALZHEIMER'S DISEASE AND NORMAL AGING ASSESSED USING BOUNDARY SHIFT INTEGRAL, AUTOMATED HIPPOCAMPAL AND MANUAL ENTORHINAL CORTEX VOLUMETRY

Frank Ezekiel[1], Norbert Schuff[1], Meera Krishnan[1], Diana Sacrey[1], William J. Jagust[2], Helen C. Chui[3], Bruce L. Miller[4], Howard L. Rosen[4], Michael W. Weiner[1]

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Background: Previous investigators have measured longitudinal change of brain structure in Alzheimer's disease (AD) and normal aging using different methods, on different populations. This has made it difficult to compare methods and results.

Objective: To measure the longitudinal rate of brain atrophy using the boundary shift integral (BSI) method and by hippocampal and entorhinal cortex (ERC) volumetry.

Methods: Nine cognitive normal (CN) elderly and eight AD patients (MMSE: 22.5 ± 4.4), matched for age and sex had T_1-weighted and T_2-weighted MRI scans twice, approximately 1.8 ± 0.5 years apart. BSI was measured using the method of Fox et al. Hippocampal volumes were measured using an automated method. ERC was measured manually on coregistered T_1 MRIs. Effect sizes and receiver operator characteristic (ROC) analysis were performed to compare the methods in terms of sensitivity and specificity to classify AD from CN.

Results: Atrophy rates of hippocampus achieved the best effect size of 2.4, followed by ventricular BSI and ERC rate, which both achieved an effect size of 1.98, while cortical BSI had an effect size of only 0.6. Furthermore, effect sizes of longitudinal measures were always substantially higher than the effect sizes of the corresponding cross-sectional measures. An area under the ROC curve of 1.0 was achieved using hippocampal atrophy rates. The ROC area was 0.95 for rates of ERC atrophy and 0.93 for ventricular BSI, while the other measures yielded substantially smaller ROC areas.

Conclusions: These data, on a small sample, suggest that longitudinal measurements of hippocampal atrophy have a greater effect size and therefore have greater statistical power to measure treatment effects than longitudinal measurements of ERC or BSI. We are extending comparisons to much larger samples. Furthermore, longitudinal measurements provide greater discrimination between AD and control than do measurements at a single time point.

(59) CEREBRAL PERFUSION AS A PREDICTOR OF STABILITY, DECLINE AND CONVERSION TO AD

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Background: We have previously reported that alterations in regional cerebral blood flow (rCBF) can predict future conversion to a clinical diagnosis of AD among non-demented older individuals with memory impairment (questionable AD (qAD) using CDR criteria).

Objective: To investigate whether patterns of rCBF can predict clinical stability as well as decline in such individuals.

Methods: A total of 188 subjects participated in this longitudinal study. Subjects were imaged at baseline with SPECT

and MRI, and then followed annually for a median of 5 years. Subjects were categorized into four groups according to their baseline CDR sum of boxes score (SB) and change in their SB during follow-up. Normal subjects ($n = 42$) were SB = 0.0 at baseline and remained 0.0 during follow-up. Stable subjects ($n = 40$) were qAD at baseline (SB: 0.5–2.0) and had no change in SB during follow-up. Declining subjects ($n = 67$) were qAD at baseline, had significant decline in SB during follow-up, but had SB < 4.0 and did not meet clinical criteria for probable AD (NIH criteria). AD-destined subjects ($n = 39$) were qAD at baseline, but declined during follow-up to SB > 4.0 and met criteria for probable AD. rCBF image data were analyzed using MRI guided regions-of-interest (ROI) and a voxel-based, principal components analysis (PCA). Discriminant analysis was used to test the hypothesis that rCBF can predict group membership.

Results: Differences in rCBF significantly predicted group membership using either the ROI ($P < 0.03$) or the PCA ($P < 0.03$) methods. Regions which contributed significantly to the discriminant functions included the hippocampus, the caudal portion of the anterior cingulate, and the superior temporal sulcus.

Conclusions: These data suggest that rCBF patterns can identify individuals who remain stable, those who decline, and those who progress to clinical dementia up to 5 years prior to diagnosis.

(60) FLUID REGISTRATION OF SERIAL MRI: IDENTIFYING REGIONAL CHANGES IN ALZHEIMER'S DISEASE

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Volumetric brain MRI has been extensively used to assess regional changes occurring during the progression of Alzheimer's disease (AD). With the advent of disease-modifying therapies, the need to reliably identify the earliest stages of the disease, and to understand its natural progression has become increasingly important.

Fluid registration is a non-linear matching algorithm, based on a compressible viscous fluid model, which allows localization of voxel-level changes in the brain over time. It has previously been validated for the automated propagation of baseline regions onto serial scans, thereby reducing operator time. Voxel-compression maps (VCMs) generated by this technique have been used to demonstrate presymptomatic changes both in AD and fronto-temporal dementia.

Statistical Parametric Mapping can be used to analyze these VCMs and thus to identify consistent regional differences between groups. In this study we compared presymptomatic individuals ($n = 4$), mildly affected ($n = 10$) and moderately affected ($n = 12$) subjects with AD, with groups of age-matched controls. We demonstrated significantly increased rates of hippocampal atrophy ($P < 0.001$) in presymptomatic and mildly-affected subjects with AD, compared to controls. There was a shift in the distribution of temporal lobe atrophy with advancing disease; the infero-lateral regions of the temporal lobes showed the most significantly increased rates of atrophy by the time the patients were mildly and moderately affected. Significantly increased rates of medial parietal lobe atrophy were seen at all stages, with frontal lobe involvement occurring later in the disease.

Group analysis of fluidly-registered images provides insights into the natural history of degeneration in dementing disorders such as AD, and can demonstrate changes in the brain prior to symptom onset. In addition, it may also be used for automated measurement of regional atrophy progression as an outcome measure in therapeutic trials.

(61) HIPPOCAMPAL ATROPHY IN ALZHEIMER'S DISEASE: A FOLLOW-UP STUDY

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Using quantitative magnetic resonance imaging (MRI), recent studies found atrophic changes of the medial temporal lobe structures already in early stages of Alzheimer's disease (AD). These changes were cross-sectionally correlated with the severity of dementia, which led to the hypothesis that progressive medial temporal lobe atrophy might be used as a marker of disease progression. We investigated the progression rate of hippocampal atrophy with respect to rate of clinical deterioration in 13 AD patients and 8 healthy controls using volumetric MRI. Already at baseline, the AD patients showed significantly smaller hippocampal volumes than controls. While AD—in comparison to healthy ageing—was characterized by a rapid decline of hippocampal volumes (−8.1% per year) only a moderate decrease of whole brain volumes occurred indicating that hippocampal atrophy is not merely a function of generalized brain atrophy. Progression of hippocampal atrophy but not of whole brain atrophy was significantly correlated with clinical deterioration ($r = 0.6$, $P < 0.05$). These findings indicate that progressive hippocampal volume reduction underlies clinical deterioration in AD and might serve as a morphometric index of disease progression.

(62) RATES OF ENTORHINAL CORTEX AND HIPPOCAMPAL ATROPHY CORRELATE WITH INCREASING SEVERITY OF ALZHEIMER'S DEMENTIA

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Background: Pathological studies have suggested that the site of earliest involvement in AD is entorhinal cortex (ERC), while hippocampus is affected at a later stage. In-vivo studies have not yet shown direct evidence for this.

Objective: To investigate the relationship between rates of atrophy of ERC and hippocampus with severity in cognitive impairment. Because ERC is thought to be involved earlier in AD, we also tested the hypothesis that atrophy rates are faster for ERC than for hippocampus as dementia severity increases.

Methods: Eight patients with AD (76 ± 6 years), four non-demented subjects with cognitive impairments (CI: 70 ± 9 years), and 18 cognitively normal subjects (CN: 77 ± 5 years) had MRI scans and clinical evaluation twice, 2.1 ± 0.9 years apart. ERC was manually traced and hippocampus measured automatically on T_1-weighted.

MRI results: Atrophy rates of the right ERC were significantly associated with diagnosis ($P < 0.0004$), showing annual changes of $14.6\% \pm 20.8$ in AD, $0.8\% \pm 4.1$ in CI, and $0.1\% \pm 4.0$ in CN. Similarly, atrophy rates of right hippocampus were also significantly associated with diagnosis ($P < 0.0001$), showing annual changes of $5.2\% \pm 6.2$ in AD, $0.3\% \pm 1.8$ in CI, and $0.4\% \pm 1.2$ in CN. As shown in the figure (solid line and circles: ERC; dashed line and open circles: hippocampus), decreasing MMSE scores (assuming a linear relationship with impairment) were significantly correlated with increasing atrophy rates in ERC ($r = 0.6$, $P < 0.0005$) and hippocampus ($r = 0.40$, $P < 0.001$). Furthermore, the rate of atrophy per unit decrease of MSSE was substantially ($P = 0.005$) higher for ERC (1.5% per years $\pm$ 0.5) than for hippocampus (0.3% per years $\pm$ 0.1).

Conclusion: Higher atrophy rates of ERC than of hippocampus with increasing cognitive impairment is consistent with a curvilinear decline of ERC and hippocampal volumes as AD progresses and furthermore, that ERC atrophy may precede hippocampal atrophy. ERC atrophy might therefore be a more sensitive measure of AD than hippocampal atrophy.

(63) CORRECTING BRAIN VOLUMES FOR TOTAL INTRACRANIAL VOLUME: APPLICATIONS IN SERIAL STUDIES OF ALZHEIMER'S DISEASE

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Background: MR-based volumetric measures of cerebral structures are increasingly used for diagnosis and for measuring disease progression in neurodegenerative conditions. Geometric instability in acquired MR (fluctuations in voxel size) is an important concern for the accurate determination of volume change. Total intracranial volume (TIV) has the potential to be used longitudinally to correct for voxel size fluctuations.

Objective: To assess whether TIV correction improved the reliability of measures of progression in controls and patients with Alzheimer's disease (AD).

Methods: Ten patients with AD and 10 healthy controls each had at least two T_1-weighted volumetric MRI approximately 1-year apart. Whole brain volumes were measured and normalized for TIV. Rates of atrophy were calculated from the whole brain volumes, with and without correction for TIV.

Results: Brain volume and TIV were highly correlated ($r = 0.88$). Correcting serial brain volume measurements for TIV in the controls reduced inter-scan differences (coefficient of variation reduced from 1.0 to 0.5%, $P = 0.002$). Rates of brain atrophy were significantly different between patients with AD and controls. ($C = 1.2\%$; AD $= 2.4\%$; $P = 0.05$). TIV normalization improved the differentiation of rates of atrophy between the groups ($C = 0.6\%$, AD $= 2.4\%$, $P = 0.004$).

Conclusions: Correcting serial scans for TIV reduces inter-scan volume differences, which may be due to fluctuations in voxel size. We demonstrate that atrophy rates derived from TIV-corrected brain volumes, as opposed to uncorrected brain volumes, allow better differentiation between groups of patients with AD and controls. Correcting brain volumes for TIV may be useful in progression studies in AD.